



**SKIN MANIFESTATIONS OF  
INTERNAL DISORDERS**



SKIN MANIFESTATIONS  
*of*  
INTERNAL DISORDERS  
(DERMADROMES)

*By*

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WITH 386 TEXT ILLUSTRATIONS  
AND 6 COLOR PLATES

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Dedicated

to

My Wife

Marie Wiener M D



## PREFACE

Physicians have always been intrigued by the skin manifestations of internal disorders. An early diagnosis of diabetes from the inconspicuous tan of carotenemia the estimation of the date of a heart attack from the position of the cross furrows on the fingernails the suggestion of Addison's disease by the pigmented palmar creases of a patient who has no other complaint than fatigue the intimation of pregnancy of a young woman who wants the little skin tags removed which suddenly appeared on her neck these and other diagnostic feats have been a constant source of professional satisfaction

Before the advent of modern diagnostic methods the clinicians probably knew better how to read diagnosis and prognosis from the skin than the present generation which is accustomed to trust objective laboratory methods more than observation It would be utterly ridiculous to minimize the progress of medicine and to long for the good old times when the doctor his chin on the golden head of his cane sat at the patient's bed and watched the degrees of pallor or cyanosis or the intricacies of a rash And yet it seems that the tremendous wealth of clinical observations on cutaneous phenomena accompanying internal disease has in our time not found the attention it deserves The observations are scattered mostly throughout the internistic literature and often the descriptions have been given by men without dermatologic training The dermatologic literature which during the last thirty years has shown an increasing consciousness of the systemic relationship of the skin naturally is more concerned with the internistic background of the dermatoses and much less with the skin manifestations of internal diseases Thus, there is sufficient justification for a survey and presentation of our knowledge in this field despite the fact that many articles and a few books have been written on the subject The articles usually deal with but a few of the well known skin manifestations, such as the diabetic dermatoses or the pigmentations in Addison's disease Only a few papers comprise several or many groups of the internal disorders, among the important being those of Joseph Jadassohn<sup>1</sup> Bruno Bloch,<sup>2</sup> Weidman U Wile,<sup>3</sup> Wise and Wolf<sup>4</sup> Lutz,<sup>5</sup> and Bertha Ottenstein<sup>6</sup> Remarkably few books have been written on the subject Bulkley<sup>7</sup> published a small volume which contains many valuable observations and in spite of its disregard for the literature

Jadassohn, J Hautaffektionen bei Stoffwechselanomalien, 5. Internat. Dermat. Kongr. Berlin, 1904, Berlin, 1906, A. Hirschwald.

<sup>2</sup>Bloch, B Haut und Stoffwechsel, Verhandl. d. Gesellsch. f. Verdauungsphysiol., 1925

<sup>3</sup>Bloch, B Einige über die Beziehungen der Haut zum Gesamtorganismus, Klin. Wochenschr. 1: 132-150, 1922.

<sup>4</sup>Weidman, F D Dermatologic Expressions of Internal Medical Diseases, California & West. Med. 33: 806, 1930

<sup>5</sup>Wile, U J Cutaneous Manifestations of Systemic Disease Ann. Int. Med. 8: 1103-1112, 1932.

<sup>6</sup>Wile, U J and Wolf, J Skin Diseases in Their Relation to Disturbances of Other Organs, J. Michigan M. Soc. 24: 437, 1937

<sup>7</sup>Lutz, W Hautkrankheiten und Gesamtorganismus II Dermatologica 79: 44-111, 1939

<sup>8</sup>Lutz, W Vergleichend konstitutionell bedingte Dermatosen, Dermatologica 81: 122, 1940.

<sup>9</sup>Ottenstein, B Hautkrankheiten und Gesamtorganismus, Dermatologica 87: 41-64, 1943

<sup>10</sup>Bulkley, L The Relations of Diseases of the Skin to Internal Disorders, New York, 1908, Reuben Co.

and its lack of pictures makes still interesting reading. Later attempts included the books of J. K. Mayr<sup>11</sup> W. Lutz<sup>12</sup> and the compendious monograph by S. Jansen and Lutz<sup>13</sup>. Of course a large number of monographs deals with parts of the subject. Endocrinology and the skin has been dealt with in treatises by J. Strandberg and in a very fascinating way by Muisio Fournier Piaggio Blanco and Cervino<sup>14</sup>. Lately E. Urbach<sup>15</sup> has given a brilliant presentation of the relationship of skin diseases to metabolism and nutrition, a field to which he already had made so many original contributions. However a recent systematic presentation of the skin manifestations of internal disorders does not exist and the author hopes to fill this gap with the present book.

While preparing this book the author became aware of the fact that the term skin manifestations of internal disorders is not only lengthy but does not cover all the dermatoses which may be part of a syndrome. The term skin manifestation implies the existence of something which manifests itself on the skin, thus it is perfectly correct to say that the typhoid fever infection manifests itself on the skin with the rose spots. However there are dermatoses which accompany diseases of other organs with some regularity without being more than an accompaniment at least to our present knowledge. Pseudoxanthoma elasticum for example is often associated with angioid streaks of the retina. We do not know what manifests itself in the phenomenon of pseudoxanthoma elasticum but we know that this dermatosis is the skin part of a syndrome known as Gröenblad Strandberg syndrome. It was felt that there is need for a short word expressing precisely and noncommittally such a relationship. The word *dermadrome* (literally fellow traveler on the skin) which means the skin part of a syndrome was therefore coined and used throughout this book not only for accompaniments but also as a synonym for true skin manifestations of internal disorders.

Within reasonable limits the author has tried to cover the field which the title of the book indicates. He has however abstained from forcing into a chapter such subjects which represent entire divisions of medicine as syphilis though it cannot be denied that the syphilitic dermatoses are an outstanding example of the dermatoses of a systemic infection. The skin manifestations of allergy and the nutritional disturbances in infancy have not been included partly for the same reason and partly because excellent modern monographs on these subjects are available. Some gaps in the presentation of the field may have been caused by the disruption of the supply of foreign medical periodicals during the war and also by the difficulty of obtaining those articles which appeared in the less well-known languages or in remote countries. If the original article could not be consulted abstracts were used if possible. Most of these abstracts are contained in the Zentralblatt für Haut und Geschlechtskrankheiten

<sup>11</sup>Mayr J. K. Die Kruckstungen an der Haut bei inneren Krankheiten chronisch der durch Behandlung bedingten Schädigungen. Leipzig, 1920 F. O. W. Vogel.

<sup>12</sup>Lutz W. Stoffwechsel und Haut. Handb. d. H. u. Ok. 8 253-353 1939.

<sup>13</sup>Jansen S. and Lutz, W. Hautveränderungen bei inneren Krankheiten. Handb. d. H. u. Ok. 4 440-480 1933.

<sup>14</sup>Strandberg, J. Haut und innere Sekretion, Handb. d. H. u. Ok. 8 104-252 1939.

<sup>15</sup>Muisio Fournier J. C. Piaggio Blanco R. A. and Cervino J. M. Piel y ateros y glándulas endocrinas, Baerens Aires, 1944, Balva Editores.

relatively few in *The Journal of the American Medical Association* the *Yearbooks of Dermatology* the *Archives of Dermatology and Syphilology* the *Archives of Internal Medicine* and some other periodicals. The use of abstracts from the *Zentralblatt* has in most cases been indicated in the bibliography by the addition of Zbl with the numbers of the volume and the page. Since these are mostly articles which are difficult to obtain it was thought that this addition might facilitate further research.

The author hopes that his book will be read or consulted by dermatologists as well as by internists and general practitioners. This expectation necessitated that facts which may seem trivial and superfluous to one group of the prospective readers require discussion for the sake of another group. Therefore the author asks for indulgence for the introductions to such topics as scarlet fever leukemia gout and other diseases which are more familiar to the internist than to the dermatologist.

The system of bibliography here used has abandoned the usual listing of the references at the end of the chapters or at the end of the book. The author felt that the titles of the sources and the names of the authors who have made the observations should not be hidden away but shown on the same page where their work is mentioned. This was done not only as a matter of fairness to the authors but also to induce the reader to look up some of the original sources himself. This system of references on the same page with consecutive numbering which had been used for a long time in the periodical publications of the American Medical Association has recently been adapted to medical books.<sup>24</sup>

A glance at the table of contents shows that the book does not primarily deal with the internists' background of skin diseases. However occasional remarks and short paragraphs on this subject have been included if it seemed warranted.

With this book, the author wants to strengthen the idea of the unity of medicine. It does not seem unnecessary to work for this idea in order to help to prevent that the medical specialties grow away from each other and lose sight of other fields and of the system as a whole. Nature is neither husk nor kernel she is all in one.

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<sup>24</sup>Urbach, S.: *Skin Disease, Nutrition and Metabolism*. New York, 1946, Grune & Stratton, Inc.

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## ABBREVIATIONS

Zbl after title means that the abstract in the Zentralblatt für Haut und Geschlechtskrankheiten has been used.

Handb. d. H. u. Gk. stands for Handbuch der Haut und Geschlechtskrankheiten, herausgegeben von Joseph Jadassohn, Berlin, Julius Springer.



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## INTRODUCTION

Skin manifestations of a disease of another organ or an organ system may be *specific* or *nonspecific*

*Specific* dermadromes contain the same pathological elements which cause or characterize the lesions of the disease in another part of the body system. Skin metastases of a malignant tumor of the stomach repeat the adenomatous structure of the primary growth. Leukemic infiltrations of the skin consist of the typical leukocytes of the leukemia and hematogenous tuberculosis of the skin is still as much tuberculosis as it was in the tubercular focus from which it descended.

Much more frequently the dermadromes are *nonspecific*. Neither anatomy nor course seem to repeat the primary disease. The pruritus in Hodgkin's disease sweating in tuberculosis or in arsenic poisoning are such nonspecific manifestations. They are cutaneous responses to pathologic stimuli and since the means of expression which the skin possesses are limited heterogeneous causes may produce identical skin symptoms. Pruritus, perspiration erythema pigmentation hypertrichosis allergic inflammation keratosis are some words from the language in which the skin answers if it is provoked. It follows that a conclusion as to the underlying condition from a nonspecific symptom like pruritus alone is not possible. In other words the nonspecific dermadromes are *not diagnostic* they are merely *suggestive* of a diagnosis. They have to be weighed together with other manifestations to make a diagnosis possible. Naturally this limits the practical value of the knowledge of the cutaneous symptoms of internal disorders. However the same is true of the symptomatology of all other fields. A diagnosis is usually not based on one specific symptom but rather on a characteristic pattern formed by a *variety* of nonspecific manifestations.

Another fact increases the difficulty. Hardly one dermadrome is an *invariable* companion of an internal disorder. The melanosis in Addison's disease is missing in a considerable percentage of the cases. Pruritus commonly encountered in Hodgkin's disease diabetes gout arsenic poisoning may be absent. Even the rash in measles or chicken pox may not appear. Jaundice in obstruction of the common duct seems to be one of the few inevitable dermadromes.

Before entering the discussion of the skin manifestations of internal disorders, the reader might well ask which *criteria* permit the assumption of such a relationship.

There is no doubt about the relation of the specific dermadromes to the internal companions to which they are *subordinated* as is the case in focal infection or *coordinated* as in syphilis. For the investigation of the status of the nonspecific dermadromes the statistic method is the most important one. If pruritus is associated with diabetes in a larger percentage than with a normal control



group we are justified in calling pruritus a dermatome of diabetes. This apparently simple method naturally has all the fallacies connected with statistics. The number of cases must be sufficiently large. The character of the material must be considered. For example in the case of diabetic pruritus it is important whether the patients are hospitalized or ambulatory, controlled or uncontrolled diabetics, wealthy or poor. The control group must be large and its character should correspond to the probed group of diabetics in age, sex, racial and social make up, etc. It is of greatest importance whether observations have been gathered from records which had been written by another physician or whether they have been collected by the author himself with the purpose of his investigation in mind. Generations of interns may not have paid much attention or at least may not have entered a note on the presence or absence of pruritus or epidermophytosis in the diabetic patients. Then a man becomes interested in the question and he starts to ask patients and to make notes. This may cause the apparent incidence to soar.

If rare dermatoses occur in association with relatively rare internal diseases the relationship can be accepted if a few cases only have become known. Examples are the few instances of dermatitis herpetiformis after total parathyroidectomy or cutis verticillata gyrata in acromegaly or acanthosis nigricans in visceral carcinoma.

Other criteria of a relationship between a dermatosis and an internal disorder are disappearance of the former following successful treatment of the latter as it occurs in some cases of hypertrichosis of ovarian origin. The close parallelism between the ups and downs of the disease and the skin changes is sometimes a good evidence of a relationship. This can be observed in the dermatoses of the legs which sometimes accompany periods of circulatory decompensation.

# Skin Manifestations of Internal Disorders

## CHAPTER I

### THE DERMADROMES OF SYSTEMIC INFECTIONS

#### Hematogenous or Metastatic Infections. Microbids (Bloch <sup>1</sup>)

The ectogenous infections of the skin for example impetigo erysipelas, and the superficial mycoses do not belong to the subject of this book. If however the micro-organisms travel with the blood stream from an infectious focus in the system to the skin and cause there corresponding manifestations of the infection the resulting dermatosis is a dermadrome of the systemic infection and requires discussion.

When as far back as 1915 J. Jadassohn<sup>2</sup> gave this definition of hematogenous skin infection he wisely chose the word corresponding. He was aware of the fact that the hematogenous infections are not identical with the primary lesion. They differ more or less, although a relationship can usually be found. The various hematogenous infectious lesions the microbids (Bruno Bloch) or the *ids* for short have been shown to have a number of common features. The study of the experimental hematogenous infection of the guinea pig with fungi proved particularly instructive for the understanding of the pathogenesis of the microbids in general.

**Experimental Hematogenous Fungus Infection.**—Saevens<sup>3</sup> in J. Jadassohn's clinic in Berne, Switzerland was the first to show that a single intracardial injection of an emulsion of spores of *Achorion quinckeanaum* and *Trichophyton gypsum* can produce in the guinea pig several crops of fungi-containing clinically typical skin lesions. These mycotic lesions healed spontaneously after about three weeks. The hematogenous skin infections differed little from primary skin infections. The animals developed a generalized specific skin allergy toward fungi just as they did after ectogenous infection. The hematogenously produced lesions appeared to have a certain predilection for shaved or traumatized<sup>4</sup> sites.

<sup>1</sup>The hematogenous infections of the skin have been studied intensively by Joseph Jadassohn and Bruno Bloch and their schools.

<sup>2</sup>Bloch, B. Les microbides cutanés. Arch. dermat.-syphilit. Hôp. St. Louis 4: 187-194, 1932.  
<sup>3</sup>Saevens, J. Experimentelle Beiträge zur Dermatomykosenlehre. Arch. f. Dermat. u. Syph. 121: 161, 1918.

<sup>4</sup>Kogel, F. Lokales Inoculierungsmittel bei hematogenen Infektionen. Arch. f. Dermat. u. Syph. 120: 332-345, 1936.

M. Sulzberger<sup>20</sup> then in Bloch's clinic could show that no actual mycotic granuloma of internal organs could be produced by intracardial injection of *Achorion quinquevittatum* in spite of the presence of fungi in the spleen and in other organs. The histologic examination of hematogenous skin lesions demonstrated that the fungi could be found mainly in the stratum corneum and in the hairs not in living tissues<sup>21</sup> leaving no doubt about the *selective localization* or *dermatotropism* of certain microbes.

**Foci**—The foci from which the microbes may enter the blood can be found in many organs. Streptococci and staphylococci foci are known to occur in dental granulomas, in abscessed teeth and in many other organs. The lungs and the mediastinal lymph nodes may be the foci for the hematogenous spread of tuberculosis. The skin itself may be the site of primary foci which are able to emit fungi, tubercle bacilli and other microbes into the system. Trauma, inflammation with hyperemia and suppuration (kerion) fever and intercurrent infections like colds or influenza are likely to have an influence on the *mobilization* of microbes from a primary focus. X-ray treatment of a primary trichophytic lesion and injection of trichophytin are named among the factors which have been seen to provoke trichophytids.<sup>22</sup> The traumatization of gonorrheic infiltrates or tuberculous tissues may cause a crop of hematogenous skin infections. All infectious processes which lead to erosion of blood vessels and lymphatics may lead to metastatic infection. Jadassohn<sup>23</sup> stresses the importance of all influences which weaken the systemic resistance. The possibility of a release of bacteria from a silent focus into the blood stream apparently without any of the known causes must be considered.

The *presence of microbes in the blood* in cases of microbids has been demonstrated for fungi by M. Jesmer<sup>24</sup> and others<sup>25</sup> and for tubercle bacilli by Kren and Löwenstein<sup>26</sup> Konrad<sup>27</sup> and others. Many similar findings especially of pyogenic bacteria are known.

**Metastatic Sites.**—The experimental fungus infection shows that the microbes do not stay and develop wherever they are deposited by the blood stream. The fungi prefer the keratinized tissue other microbes favor other sites. Tuberculids are seen most often on the extremities especially the legs probably due to the tendency to stasis in the extremities. Some epidermophytids have a special tendency to form eczematoid epidermophytids in the palm. Traumatized or inflamed areas attract fungi, spirochetes, pyogenic bacteria or

<sup>20</sup>Sulzberger, M. Pathogenesis of Trichophytids. The Spontaneous Passage of Fungal Elements From the Primary Lesion I to the Circulating Blood, Arch. Dermat. & Syph. 18: 891-901, 1933.

<sup>21</sup>Bloch, B. Abgrenzung und experimentelle Biologie der Dermatomykosen, Handb. d. H. Ok. 11: 300-377, 1935.

<sup>22</sup>Jadassohn, J. Importance of Immune Biologic Processes in Morphology of Skin Lesions, Arch. Dermat. & Syph. 21: 345, 1930.

<sup>23</sup>Jesmer, M. Trichophytid. Zbl. H. 449, 1934.

<sup>24</sup>Bloch, B. Die Trichophytide. Handb. d. H. Ok. H. 644, 1935.

<sup>25</sup>Kren, O. and Löwenstein, E. Die Bedeutung der Bakterien bei den verschiedenen Formen der Hauttuberkulose und bei Lupus erythematodes, Arch. f. Dermat. u. Syph. 106: 375-399, 1933.

<sup>26</sup>Konrad, J. Demonstration of Tubercle Bacilli in Circulating Blood (Löwenstein Method) Dermat. Woch. 68: 80-87, 1933.

tubercle bacilli. The appearing of syphilitic papules in areas of friction and maceration is well known <sup>8,29,37</sup>



Fig. 1—Trichophyton (Courtesy Division of Dermatology Department of Medicine, University of Chicago.)

Wladawski, W. Tierexperimentelle Untersuchungen über Mykosen traumatisch bedingte Hauterkrankungen Arch. f. Dermat. 8 pp 189; 224-233, 1920.

Common sites of microbic deposits are the vascular nets which surround the *hair follicles*. Hematogenous follicular rashes (licheni) are well known in mycoses, syphilis, tuberculosis and other diseases. J. Jadassohn<sup>21</sup> suggested that the fungi in the blood stream like to settle in the follicles because of the close relation to the hair their preferred medium. Microbic metastases in the capillary loops of the *papillae* may cause scarlatiniform rashes, roseola, or papules. Those in the *subcutis* produce nodules of all sizes. The *larger blood vessels* especially in the subcutis are another target. Thus reticulated livedo racemosa like forms may ensue as is occasionally seen in syphilis. The *venae* may be the origin of deep nodules in late syphilis. J. Jadassohn<sup>22</sup> felt that these infections originating in the walls of veins (Volterra<sup>23</sup>) do not stem directly from the blood in the veins but rather from the blood in the *vasa vasorum*. Thus the point of attack contributes to shape the clinical pictures of which lichenoid follicular rashes, roseola and erythema nodosum are the main representatives.

**Other Characteristics of Hematogenous Skin Infection.**—Perhaps even more important than the site of the microbic metastasis is the *allergic response* of the skin. Almost always some allergy has already developed when from the primary focus of infection microbes are disseminated through the circulation. The specific skin reactions are mostly positive. Bloch<sup>1</sup> and other authors have seen fresh crops follow injections of specific allergens. The allergic reactions in hematogenous skin infections may, though frequently strong be weak or negative as suggested by the so-called anergic tuberculids. In other instances of weak allergy the metastatic lesion shows features of a primary infection that is, greater abundance of microbes and nonspecific inflammation. Miliary tuberculosis and early syphilis are examples. As the immune biologic reaction grows in strength fewer germs and increasingly tuberculoid histologic structures will be found. This is the case in tuberculous lichenoides, in tuberculoid leprosy, in leishmaniasis, and especially in the late stages of syphilis. Syphilids are rich in spirochetes when the luetin allergy is lacking and poor when it is present.<sup>24</sup> Not only the skin may have changed its specific reaction since there are many indications that the microbe itself may have become allergic in the course of its contact with the host. For instance spirochetes and other protozoa may become resistant to previously effective drugs.

General *septic symptoms* like malaise, chills and fever and swelling of the lymphatic nodes and joints may accompany the crops.

The general course of hematogenous infectious skin eruptions is usually benign. There is a marked tendency to spontaneous involution as is the case in some tuberculids.

The *distribution* of hematogenous infectious dermatoses exhibits some characteristic features. One would expect that microbes which invade the blood stream especially the pulmonary veins and the large arteries, would land in fairly even distribution in the entire skin. This is not always the case. Syphilitic

<sup>21</sup>Jadassohn, J. Hematogenous Infectious Diseases of the Skin, Arch. Dermat. & Syph. 21: 370-371, 1930.

<sup>22</sup>Volterra, M. Lupus nodularis hematogenus Ursprung, Arch. f. Dermat. Syph. 63: 21, 1904.

roseola the acute exanthema, and other blood borne infections, in spite of the great number of individual lesions show modifications in their distribution caused by peculiarities of the terrain. Other examples of uneven dissemination are the circumoral pallor in scarlet fever the predilection of the upper half of the body in variola and varicella the often exclusive localization of papulonecrotic tuberculids on the extremities and of some trichophytids on the palma. Of course symmetric dissemination and the appearance in crops as seen in secondary syphilids or in acute exanthema suggest hematogenous infection but asymmetry does not rule it out. The sarcoids and tertiary syphilis are usually asymmetric. Paucity of microbes in the blood stream or paucity of those germs which can succeed in setting up a hematogenous skin infection may explain the lack of symmetry.

**Pyogenic Focal Infection**—The hematogenous skin infections from streptococci or staphylococci foci particularly in the teeth and tonsils have so far not found the same interest among dermatologists as the corresponding manifestations in the other organs among other specialists. It appears that there exist two groups of investigators who do not seem to know much of each other the dermatologists with the microbids on one side and the proponents of the classical focal infection on the other. The former frequently show a skeptical attitude toward the achievements of the latter who in turn often ignore the work of dermatology in this field.

Both schools struggled with the question of whether toxic products of microbes are able to produce specific dermatomes or whether hematogenous infection with living germs is a necessary prerequisite.

Today the importance of the question has diminished since it is known that toxins from microbes may produce lesions similar to those of living bacteria and that absence of microbes in microscopic and cultural tests does not prove that the questioned lesions are not caused by germs. J. Jadassohn<sup>22</sup> emphasized on several occasions the clinical similarities of many hematogenous toxic and hematogenous infectious dermatomes. Purpura is an example of a dermatome common in infection as well as in poisonings.

From the pathogenesis of the tuberculids and trichophytids which are more often infectious than toxic, and also from other observations we may conclude that the secondary foci are likely to be of a bacteremic and metastatic nature although bacteria are rarely found in the secondary skin lesions.

<sup>22</sup>The last comprehensive review of the field of focal infection by Outzeit and Parade<sup>23</sup> (1930) with bibliography of about 1,500 items, does not mention the names of J. Jadassohn, H. Block, nor three of their pupils. And this in spite of the fact that most of these authors worked for long time in the same block in the University Hospital in Breslau, Germany.

<sup>23</sup>Outzeit, K. and Parade, G. W. Focal Infection, *Ergebn. d. inn. Med. Kinderh.* 87: 613-722 1930.

<sup>24</sup>Jadassohn, J. *Hematogene Dermatosen* Zbl. 88: 602, 1931.

The conception of focal infection is based on the work of Pflüger<sup>31</sup> Hunter<sup>32</sup> Billings<sup>33</sup> and particularly Rosenow<sup>34</sup> but the older literature also contains much material pointing in the same direction. The term *focal infection* (focus of infection) was coined by Billings<sup>33</sup> who defined it as a circumscribed area infected with pathogenic microorganisms and usually communicating with a mucous or cutaneous surface causing secondary foci through various ways especially through the blood stream. Later the definition became more precise. Focal infection may now be defined as a *disease caused by a chronic focus of infection which harbors pathogenic microorganisms and though often dormant itself continuously or continually causes remote symptoms* (modified after Gutzeit and Parade)<sup>35</sup>. The teeth and the tonsils are the main sites of the primary foci<sup>36</sup> followed in frequency by the paranasal sinuses the middle ear the bronchi the uterus and



Fig 2.—Focal infection. Sudden and often recurrent crops of acute circumscribed erythema of the cheek. Attacks ceased entirely after extirpation of chronically infected appendix.

adnexa the prostate the intestinal tract and some other less common sites like varicose ulcers and bronchiectases. Rosenow<sup>37</sup> to give an example found tonsillary foci in 51 per cent of his patients with arthritis and in 74 per cent of those designated as having infective lesions of the skin. In the latter group 77 per cent had infected teeth.

<sup>31</sup>Pflüger H. Ueber die Beziehungen einiger septischer Krankheitszustände zu chronischen Infektionen der Mundhöhle. Verhandl. d. deutsch. Gesellsch. f. inn. Med. 26 Kongr. p. 831 1900.

<sup>32</sup>Hunter W. Role of Septic and Anthropic in Medicine. Lancet 1 77 1911.

<sup>33</sup>Billings F. Focal Infection. Lane Medical Lectures, New York 1910, D. Appleton & Co.

<sup>34</sup>Rosenow E. C. Zusammenfassung der Forschungsergebnisse über Fokalfunktion und lokale Lokalisation, Med. Klin. 27 335, 1931.

<sup>35</sup>Rösch R. Ueber Fokalfunktion. Verhandl. d. deutsch. Gesellsch. f. inn. Med. Kongr. 81 433-494, 1939.

<sup>36</sup>Rosenow E. C. Herdinfektion und elektive Lokalisation, Verhandl. d. deutsch. Gesellsch. f. inn. Med. Kongr. 62: 408-930.

The bacteria which cause focal infection are predominantly streptococci especially the viridans type although staphylococci *Escherichia coli* gonococci and others also have significance. Billings<sup>44</sup> and Rosenow<sup>45</sup> showed that the streptococci in the living tissue of the primary foci can change their characteristics in various ways. There were changes in virulence changes in cultural behavior and even transition into other forms for example from streptococci into pneumococci. The observations on character and extent of such mutations are still controversial, but the majority of the bacteriologists recognize them in principle. The explanations for the emission of bacteria into the circulation in crops have been mentioned in the first half of this chapter. The finding of streptococci in the blood<sup>46</sup> is relatively infrequent, and there are many series of observations with entirely negative results. The probability of finding small numbers of bacteria in the blood is small. The paucity of germs in the blood distinguishes focal infection from true sepsis. It is well that Billings<sup>44</sup> changed the misleading term oral sepsis to focal infection.

A most controversial subject was and still is Rosenow's<sup>47</sup> theory of the *elective localization* of the microbes especially the streptococci. Rosenow<sup>47</sup> who considers the assumption of an elective localization as basic in his work showed in a very large series of controlled experiments that streptococci isolated from primary foci had a surprising tendency to produce lesions in animals which corresponded to the secondary lesions seen in the patients from whom the strain was derived. Thus for example streptococci isolated from teeth and other primary foci in 1,539 cases of ulcers of the stomach and duodenum produced in 65 per cent of the animals which had been infected intravenously comparable stomach or duodenal lesions. Other examples of elective localization are the tendency of green producing streptococci to produce lesions in the cardiac valves and of hemolytic streptococci to localize in the joints. The percentages in which lesions could be produced in the rabbit were mostly around 60 often higher rarely lower. Thus in 60 per cent of nine cases of erythema nodosum and of twenty nine cases of herpes zoster comparable skin lesions were produced in the rabbit. These findings were startling. The experiments were most expertly executed and the numbers of cases and controls, for example 723 cases of arthritis, 206 cases of ulcerative colitis, were large. One would think that Rosenow's<sup>47</sup> impressive material should have settled the question of elective localization in a positive sense once and forever. However while confirmations were forthcoming<sup>48</sup> many investigators among them men who had been trained by Rosenow failed to corroborate his results or obtained smaller percentages.<sup>49</sup> Particular care was taken by Von Albertini and Grumbach.<sup>50</sup> These authors could find no definite proof for the existence of an organotropism of the streptococci. They believe that the individual resistance of the animals and not the selective organotropism of the microbes, decides whether a localized abscess or a generalized sepsis will follow the injection of

<sup>44</sup>Wilder, R. L. and Jordan, W. H. Multiple Oxyuriasis. Manifestation of Focal Infection. Arch. Dermat. & Syph. 8: 31-33, 1932.

<sup>45</sup>Axel, Axel. Focal Infection, Schweiz med. Wchnschr. 71: 1365-1368, 1941.

<sup>46</sup>Von Albertini, A. and Grumbach, A. Focal Infection, Schweiz med. Wchnschr. 68: 1309-1312, 1938.



cultures. The authors emphasize the fallacies resulting from comparing secondary lesions in an animal which had not been infected before and which receives a single massive dose of bacteria with secondary infection in man where the dissemination of microbes probably occurs continually and allergy has had a chance to develop. Von Albertini and Grumbach's<sup>40</sup> experiments did not deal with skin diseases. The role of specific allergy in streptococcal infections has been demonstrated and emphasized by many observers. In proper concentration skin tests with autogenous vaccine can be made and therapeutic effects reached. Humoral antibodies have been demonstrated. However agglutination precipitation and other tests with hyperimmune sera which had proved of great value in Rosenow's hands have not been found suitable by other authors because of the pronounced tendency of the streptococci to spontaneous agglutination.<sup>41</sup> Intercurrent infections climate, menstruation nutrition endocrine and other factors may also modify the allergic reactions.

**Diagnosis**—Many authors stress the importance of a history of frequent colds recurring tonsillitis<sup>42</sup> postnasal dripping occasional stiff neck, myositis arthritis, transitory tenderness in various joints neuritis, endocarditis appendectomy and other episodes of pyogenic infections. Of course the history only suggests focal infection and it constitutes good grounds for a careful investigation.<sup>43</sup>

The collaboration of dentists rhinologists and radiologists is often needed. Specimens for culture should be taken from the depth not from the surface. This is especially important with regard to the tonsils and the teeth. The most suitable medium for cultures seems to be Rosenow's brain broth. From the isolated strains, a vaccine may be made and intracutaneous skin tests done. These tests are difficult to interpret and controls are necessary. Various laboratory methods to demonstrate humoral antibodies are used by some authors but they have not gained general acceptance. The demonstration of an infectious focus does not prove that the dermatosis in question is caused by the focus.

The hematologic methods as well as exact thermometry may give hints with regard to the existence of an infection. Gutzeit and Kitchin<sup>44</sup> determine the blood sedimentation rate and expose the area suspected of an active focus to ultra short waves. An exposure of seven minutes is used for teeth and twelve minutes for the tonsils. An increase of the sedimentation rate two to four hours after the provocation is supposed to indicate activity of the focus in question. The patient should be fasting. The value of the method is still controversial since other authors obtained similar reactions from normal teeth. The advantage of the test is that it is based on the objective phenomenon of the sedimentation rate and not on more or less vague exacerbations of pain or other sensations. It seems that no absolutely reliable test for the activity of a focus has been devised.

Lyres, B. J. and Anderson, N. P. Focal Infection in Dermatology. Arch. Dermat. & Syph. 43: 431-431 1935

<sup>40</sup>Gutzeit, K. and Kitchin, W. Beitrag zur dentalen Infektion und ein neuer Weg in ihrer Diagnosestellung durch Kurzwellenprovokation, München med. Wochenschr. 84: 861-865 1937

**Treatment**—So far the best evidence to prove the causal relationship between a lesion in the skin (or elsewhere) and a focus of infection is the therapeutic effect of the elimination of the alleged focus. But even here great skepticism is necessary to prevent post hoc, ergo propter hoc conclusions since many of the conditions in question for example rosacea, eczema and lichen planus take an irregular course with frequent remissions and exacerbations. *Penicillin* and the sulfonamides are the first drugs to be tried. The eradication of dental tonsillar and other foci by surgical means should be attempted. The removal of one accessible focus does not rule out the existence of other inaccessible or undetected foci. Some foci, like endocarditic or aortic granulations, are beyond the surgical reach or would involve formidable operations which are not warranted. Conservative topical methods include local disinfectant and cleansing procedures like swabbing and gargling but they will hardly influence encapsulated foci in the depths of tonsillary crypts. The treatment with autovaccine from the recovered strains should be tried but many authors are skeptical. Ayres Jr. and Anderson<sup>6</sup> recommend gradually increasing intravenous injections of the vaccine. Nonspecific protein injections may be tried cautiously but there is some danger of producing reactions in hyperergic patients. General procedures like the salt free diet of Gerson, Sauerbruch and Hermannsdorfer, hydrotherapy and ultraviolet light have been recommended. Acute exacerbations following such apparently harmless treatments as mud baths are known. Severe exacerbations have been observed occasionally after surgical treatment of foci for example arthritic exacerbation following extraction of infected teeth or new crops of gonorrheic keratosis after dilatation of a urethral stricture.<sup>6</sup> Ayres, Jr. and Anderson<sup>6</sup> gave a long list of dermatoses suspected to be caused by focal infection. Most of the alleged conditions bear remarks like "some cases" or "occasionally" intimating how little solid ground the imposing work has yielded for dermatology. In the following list which is in part after Ayres Jr. and Anderson<sup>6</sup> the dermatoses are grouped according to the validity of the arguments claiming focal infection in their pathogenesis.

#### GROUP I

The nature of the dermatosis as hematogenous infection or toxic manifestation is well established in

- Syphilis
- Leprosy
- Tuberculosis
- Acute exanthems
- Septic premonitors
- Erythema nodosum
- Trichophytids and other mycosids, for example, in blastomycosis
- Tularemia
- Keratoderma hemorrhagicum
- Typhoid fever
- Acute exanthematous diseases and many other rashes and infections

<sup>6</sup>Shawyer M. Relationship of Arthritis to Oral Diagnosis. Defocalization and Streptococcus Vaccine Therapy. Am J Orthodontics 27: 148-154, 1941.

## GROUP II

Focal infection has been shown or suggested with more or less good reasons in some cases of:

- Acne rosacea<sup>41,42</sup>
- Herpes zoster<sup>43,44</sup>
- Erythema elevatum diutinum<sup>45</sup>
- Lupus erythematosus acutus disseminatus<sup>46</sup>
- Generalized telangiectasia<sup>47,48</sup>
- Acrodermatitis continua<sup>49</sup>
- Angioneurotic edema and urticaria<sup>50</sup>
- Alopecia areata<sup>51</sup>
- Acne vulgaris (some cases of severe involvement)<sup>52,53</sup>
- Dermatitis herpetiformis<sup>54,55</sup>
- Pemphigus<sup>56</sup>
- Nonmycotic vesicular eruptions of the hands and feet
- Purpura
- Sycosis vulgaris
- Eczema<sup>57,58,59,60</sup>
- Dyshidrosis<sup>61</sup>
- Lichen chronicus simplex<sup>62</sup>
- Chronic paronychia<sup>63</sup>
- Pyodermic ulcerations in chronic ulcerative colitis<sup>64</sup>
- Erythemas of various kind<sup>65</sup>
- Lichen planus<sup>66</sup>

<sup>41</sup>Feit, H. Lasko E. A. and Vero F. Rosacea as Bacterid From Focal Infection, J.A.M.A. 165 1723, 1935.

<sup>42</sup>Barber H. W. Dental Infection and Disease of the Skin, Proc. Roy. Soc. Med. 29 39-42, 1937

<sup>43</sup>Weidman, F. D. and Berman, J. H. Erythema elevatum diutinum, Arch. Dermat. & Syph. 23 553 1929.

<sup>44</sup>Madden, J. F. Acute Disseminated Lupus Erythematosus, Arch. Dermat. & Syph. 23 254, 1933

<sup>45</sup>Ayres, S. J. Burrows, L. A., and Anderson, N. B. Generalized Telangiectasia and Skin Infection, Arch. Dermat. & Syph. 26 50, 1933

<sup>46</sup>Becker S. W. Generalized Telangiectasia, Arch. Dermat. & Syph. 18 237 1920

<sup>47</sup>Barber H. W. and Eyre J. W. H. Acrodermatitis continua (Hallopeau) or Dermatitis Repens (Crocker) Brit. J. Dermat. 29 485 1937

<sup>48</sup>Seaton H. C. Acute Outbreaks Effects of Dental Sepais, Lancet 1932: 890-891 1932.

<sup>49</sup>Richter H. W. Focal Infection Dermat. Wchnschr 1939: 911-918, 1939

<sup>50</sup>Uhartsh, W. Dental Feknis und Hautkrankheiten, Tubingen, Dissertation, 1933

<sup>51</sup>Walsh, H. L. Specificity of Streptococcus Isolated From Patients With Pemphigus, Arch. Dermat. & Syph. 34 61 1934

<sup>52</sup>Thyer J. W. Focal Infections in the Etiology of Eczema, Ann. J. M. Sc. 179 733-737 1925

<sup>53</sup>Gomes, A. A. Eczema and Dental Disease Brit. M. J. 3 540, 1926.

<sup>54</sup>Mennelshover A. M. F. Focal Infection and chronisches Ekzem, Arch. f. Dermat. u. Syph. 187 182-193, 1929

<sup>55</sup>Kémeri, D. Ursachen d. Dyshidrosis und Ekzeme Dermat. Wchnschr 33 1615-1619 1930

<sup>56</sup>Jankehon, I. B. and Maxwell, B. F. Pyogenic Skin Lesions Accompanying Chronic Ulcerative Colitis, Ann. J. Digest Dis. & Nutrition 3 19 1936

<sup>57</sup>Roberts, H. L. Focal Infection Brit. J. Dermat. 23 319-334, 353-373, 1931

## CHAPTER II

# SYSTEMIC INFECTIONS

### Pyogenic Septicemia

Bacteremia does not necessarily produce clinical symptoms. If the microbes enter the blood stream in small numbers or only once the natural bactericidal power of the blood often disposes of them quickly as illustrated by postoperative bacteremia. If the blood is repeatedly or constantly fed with microbes from a focus of infection such syndromes as discussed under tuberculosis gonorrhea or focal infection may ensue. The massive presence of bacteria in the blood together with the outstanding clinical symptoms of characteristic fever or wasting is called septicemia or sepsis. If the development of multiple abscesses is an outstanding feature as is often seen in staphylococcic septicemia the term pyemia is often used. The term toxemia should be reserved for those conditions which are caused by bacterial toxins such as diphtheria tetanus and botulism.

The bacteria causing sepsis in two series of 150 and 255 cases<sup>a</sup> were found to be *Staphylococcus aureus* in 36.5 per cent *Streptococcus hemolyticus* in 36 per cent, and various types of pneumococci in 5.5 per cent. The rest of the list predominantly contains other types of staphylococci streptococci and the Friedländer bacillus. In other large series the staphylococcic cases outnumber the streptococcic cases 2:1 or 3:1.<sup>b</sup>

Otitis carbuncles and related conditions are listed (20 per cent)<sup>a</sup> as the most common source of sepsis, others being operation (14 per cent) infections of the genitourinary tract (9 per cent) paranasal sinuses (6 per cent) liver and gall bladder (4 per cent) and miscellaneous (19 per cent). The onset is often sudden occasionally with a severe chill and fever. Chills and spiking temperatures occur in about one-half of the cases. Sustained low fevers are common and seem to entail a higher mortality.<sup>c</sup> Usually the bacteria can be isolated from the blood. Endocarditis and metastatic abscesses are the most characteristic complications and causes of death.

Hemolysis, hemoglobin staining of the lining of the blood vessels abscesses, particularly of the lungs, reddened and hypertrophic bone marrow cloudy swelling of the kidneys liver and heart and a moderately enlarged and very soft spleen are the ordinary post mortem findings.

Since the introduction of the sulfonamides, the mortality rate has dropped from 67 to 54.5 per cent<sup>a</sup> in staphylococcic septicemia alone from 82 to 74 per cent.<sup>d</sup> The advent of penicillin has probably reduced the mortality still further.

<sup>a</sup>Neuhof H and Auden, A. H. Pyogenic Sepsis. 255 Cases, Surg. Gynec. & Obst. 77: 544-552, 1943.

<sup>b</sup>McCordell, T. H. Staphylococcic Septicemia. 35 Cases, Arch. Int. Med. 23: 1022-23, 1929.

<sup>c</sup>Shaffer D and Keefer C. B. Significance of Bacteremia, Arch. Int. Med. 60: 551-572, 1941.

**Dermadromes**—In contrast to the importance of the skin as a cause the dermadromes of septicemia are neither very common nor important compared with the severity of the general septic syndrome. There seem to be some distinguishing features between the staphylogenic and streptogenic hematogenous skin lesions (pyemids) <sup>61-63</sup>



Fig. 2—Acute streptogenic septicemia. Universal exanthem of grouped follicular hemorrhagic vesicles. Back.

**Staphylogenic Pyemids.**—Pyemids occur in about one third of the cases of staphylogenic sepsis <sup>64-66</sup>. They are probably more common than those caused by streptococci <sup>67</sup>. They appear suddenly often with chills and fever heralding a turn for the worse <sup>68</sup>. They often start with rashes consisting of macular or urticarial lesions, vesicles umbilicated pustules or bullae <sup>69</sup>. The tendency to epidermolysis is considered by some authors a characteristic but inconstant <sup>64</sup> feature of staphylogenic pyemids <sup>70</sup>. Petechiae are seldom absent <sup>71</sup>. Metastatic subcutaneous nodules and abscesses in varying sizes and depths may especially in infants give the impression of furunculosis <sup>71</sup>. Mendell <sup>62</sup> saw metastatic ab-

<sup>61</sup>Fuchs, H. *Fürstlich Dermatiden ("Pyemiden") Handb. d. H.* (H. 9, 2) 449-472, 1924.

<sup>62</sup>Robinson, S. *Septicæmia Eruptions, Urol. & Cutan. Rev.* 41: 490-492, 1927.

<sup>63</sup>Felsenthal, W. *Ueber Staphylokokkensepse, Sitz- u. d. Organe d. 3. ed.* Ohlfr. 62: 133-213, 1930.

<sup>64</sup>Fraser, K. *Metastatische Dermatoosen bei akuten bakteriellen Allgemeinerkrankungen Arch. f. Dermat. u. Syph.* 128: 386-403, 1920.

<sup>65</sup>George, P. and Ghore, H. *À propos des faits non eux de staphylocoque's.* *Presse méd.* 24: 611, 1924.

<sup>66</sup>Strandberg, J. *Ein Fall von escarpestähnlicher Pyæmie, Arch. f. Dermat. Syph.* 111: 83, 1910.

<sup>67</sup>De la, T. B. *Septicæmia, Practitioner* 187: 545-557, 1941.

<sup>71</sup>Pinger, E. *Dermatit. p. æmicæ, Wien klin. Wchschr.* 51: 543-548, 1909.

abscesses in the skin occur in 30 per cent of thirty five cases of staphylogenic septicemia. Nodules which do not form abscesses may resemble erythema nodosum<sup>78</sup> (McCrea after M. Barber<sup>75</sup>)



Fig. 4.—Facial Acute of pyogenic septicemia after tonsillitis. Erythema and scaling.



Fig. 5.—Acute staphylogenic septicemia. Erythema and scaling.

Erythema of varying shape and extent sometimes clinically identical with true scarlet fever, sometimes ocellar or exudativumult form<sup>79</sup> (Bloemen and Scalognne<sup>79</sup>) but the papules, vesicles, pustules, nodules and petechia may be seen simultaneously. Ulcerations are rare.

<sup>75</sup>Barber H. W. Oral Infection and Diseases of the Skin (a) Hosp. Rep. 77: 127-140 1927  
Barber H. W. Staphylococcus Albus Septicemia, Brit. M. J. 2: 407-409 1928

<sup>78</sup>Doherty A. Fractailiform Exanthema in Infections With Staphylococcus Aureus Hemolyticus  
Klin. Wochenschr. 17: 1849-50 1935

<sup>79</sup>Bloemen, J. J. and Scalognne H. W. Metastatische staphylogene Dermatosen. Dermat. Wochenschr. 116: 477-482 1940

The histologic findings are in line with the clinical picture: Edema and vesicles of the epidermis, miliary abscesses and papillary capillaries stuffed with cocci and surrounded by leukocytes are the dominant features.

**Streptogenic Pyemids.**—Pyemids are reported to occur earlier in the course of streptogenic septicemia than the corresponding staphylogenic eruptions. They also often start as macular, sometimes morbilliform or scarlatiniform exanthems, sometimes as less numerous or solitary erysipeloid patches<sup>71</sup> (Werther and others after Fuchs<sup>64</sup>). Papular and papulopustular<sup>72</sup> or bullous eruptions<sup>73</sup> are not rare. Most authors emphasize the hemorrhagic tendency of the streptogenic eruptions. Petechiae, especially on the lower legs, on the buccal mucosa and on other sites are common. They may become vesicular or bullous. In the mouth small yellow specks may be seen on the petechiae.<sup>74</sup> Erythema nodosum<sup>75</sup>, erythema multiforme<sup>76</sup> and local gangrene and ulceration have been described, although the tendency to suppuration is much less pronounced than in staphylogenic lesions. Microscopic examination reveals dense streptococcic emboli in the small vessels, particularly in the vasa vasorum<sup>77</sup> surrounded by leukocytic infiltrations. The damage to the vascular wall is demonstrated by the extravasation of red cells together with cocci.

Sabouraud (Kitchevatz<sup>78</sup>) is reported to have postulated a staphylo-streptogenic dermatosis analogous to the trichophytids and epidermophytids. Of course he meant a hematogenous infection originating from a pyoderma and not from septicemia, which in his days was already well known: A lichen pyodermicus, after widespread pyoderma, formed by acuminate micropapules<sup>79</sup> and resembling lichen trichophyticus or lichen scrophulosorum and also other benign pyodermids have been described under various names, although general recognition is still lacking.

It is true that within certain limits the various microbids resemble each other. M. Favre<sup>80</sup> observed in patients with furuncles and impetigo, lichenoid lesions and squamous seborrheic plaques, sometimes resembling pityriasis rosea. The author saw in a case of acute pustular acne vulgaris superficial pink lesions which at their edges consisted of very small dull papules. These lesions disappeared when the acne eruption quieted down. A series of thirty cases of "strepto-staphylotoxids" the largest so far was presented by Kitchevatz.<sup>78</sup> He too saw pyodermids after widespread streptodermas or deep ulcerating staphylodermas. The streptopyodermids, which often originate from rhagades behind the ear, itched more and were about five times as common as the staphylopyodermids. Kitchevatz<sup>78</sup> saw erythematous spots which resembled syphilitic roseola, scarlatiniform or lichenoid rashes, vesicular, papular and erysipelatous

<sup>71</sup>Nicotas, J., Mont, E. H. and Gaid, J.: Septicopyrémie streptococcique, vésicules périphériques. *Presse méd.* Paris 34: 101-102, 1912, abstracted in *Derm. t. Wchnschr.* 88: 121, 1914.

<sup>72</sup>Ullrich, H. and Flecher, M.: Ein Erythema nodosum—ähnliches gutartiges vasculäres Pykoid. *Arch. f. Dermat. Syph.* 169: 207, 1928.

<sup>73</sup>Kitchevatz, M.: Strepto-staphylococcus cutaneus, I. Teil. *Derm. Kongr. Kopenhagen*, 1920.

<sup>74</sup>Wichers, H. T. and Goebl, K.: Lichenoid Eruptionen bei Pyodermen (Lichen pyodermicus). *Beobachtungen über Komplikationen im Blut bei Staphylokokken und Trichophytenkrankheiten. Wirkung der Röntgenstrahlen.* *Dermat. Wchnschr.* 31: 272-281, 1920.

<sup>75</sup>Favre, M.: Anéodermite pigmentée et purpurique. *Nouvelles pratiques dermatologiques* Vol. V. Paris, 1926. Masson & Cie, pp. 413-420.

lesions and erythematous and herpetiform enanthemas. There were also focal reactions and the appearance of new lesions after autogenous vaccines and toxins. This relatively large amount of material has not found much attention. Occasionally benign pyoderms<sup>42</sup> "ordinary or annular exanthems"<sup>43</sup> and acne necrotica, resembling embolic infarctions have been recorded after various primary pyogenic infections. Balog<sup>44</sup> saw primary staphylogenic skin infections followed by disseminated seruglobular later umbilicated papulopustules which appeared in crops and subsided with the cure of the primary focus. The embolic-bacterial character of these benign pyemids could be demonstrated. More corroboration is needed however. The same is true of the claims<sup>45</sup> that various types of eczema among them nummular eczema are secondary pyoderms and that nonmycotic pustular eruptions of the hands and feet are pyoderms<sup>46</sup>.

In the treatment of all pyemids penicillin must be tried first.

### Subacute Bacterial Endocarditis; Endocarditis Lenta (Jaecoud Osler's Disease)

The streptococcus viridans which is the most common cause of subacute bacterial endocarditis, probably stems from focal infections of the teeth, paranasal sinuses and tonsils.<sup>47</sup> The streptococci produce vegetations on the heart valves especially in patients with congenital or rheumatic heart disease. The vegetations cause fever bacteremia myocarditis, glomerulo-nephritis and embolic metastases. There is a great variety of nervous, hematologic, and other symptoms. The onset is gradual. After an early nondescript subfebrile stage of increasing malaise the disease develops into a severe illness with many septic complications and ends fatally after several months in over 90 per cent of the cases. A small minority reaches a bacteria free nonactive stage which too terminates fatally from valvular disease and cardiac decompensation.<sup>48</sup> Penicillin in high doses over many weeks seems to be effective.<sup>49</sup>

**Dermadromes**—About one-third of the sufferers from subacute bacterial endocarditis are anemic and very pale, and later jaundiced (90 per cent).<sup>50</sup> *Swelling* is an annoying symptom. *Petechiae* well known to occur in other streptococcal infections are common. In an analysis of eighty-eight cases, they were found in the skin in 60 per cent<sup>51</sup> in the mucosae in 14 per cent, and in the retina in 11 per cent. The petechiae appear in crops and sometimes have pale yellow or necrotic centers.<sup>52</sup> Petechiae under the nails are stretched to

<sup>42</sup>Bohakewitz, S. Several Forms of Chronic Pyoderms, *Lijebn vjes.* 84: 201-207 1929 *Zbl.* 42: 421.

<sup>43</sup>Balog, P. Design Embolic Pyemid, *J. Invest. Dermat.* 8: 107 1943.

<sup>44</sup>Kryszewski, F. Eczema From Pyogenic Infection, *Pract. dermat.* 24: 208-224, 1929 *Kid.* 22: 91, 1930.

<sup>45</sup>Andrews, O. O. and Macneek, O. F. Pustular Bacterids of the Hands and Feet, *Arch. Dermat. & Syph.* 23: 437-447 1933.

<sup>46</sup>Osler, W. and Christian, H. A. Principles and Practice of Medicine ed. 15, New York, 1944, Appleton-Century Company Inc.

<sup>47</sup>Flannery, A. Penicillin, J. Practical Application, Philadelphia, 1946, The Blakiston Co.

<sup>48</sup>Widdowson, W. S. and Barker, M. Streptococcus Viridans Endocarditis Lenta, *Am. J. M. Sc.* 199: 201-212, 1939.

<sup>49</sup>Gouldberg, F. Dermatitis in Endocarditis Venosus 8: 51-53 1931 *Zbl.* 41: 78.





Fig 6.—Subacute bacterial endocarditis. Purpura.



Fig 7.—Subacute bacterial endocarditis. Purpuric rash.

short lines by the growing nail and are often called *splinter hemorrhages*. Petechiae about the nails resemble paronychia but they fail to come to a head.<sup>6</sup> If they have central blisters, they resemble erythema multiforme.<sup>6</sup> Other varieties of these eruptions have been described as papular or lichenoid,<sup>6</sup> maculo-

<sup>6</sup>Echbach H. Eruption cutanée et endocardite infectieuse prolongée. Bull. et mémoires Soc. méd. d'hôp. de Paris III 207 209 1930

<sup>7</sup>Wotter. Manifestations cutanées dans l'endocardite lente. Ehl. 28 43, 1931

<sup>8</sup>Weissenbach R. J. Martineau, J. and Briant, J. P. Manifestations cutanées de la maladie de Jaccoud-Osler. Bull. Soc. franç. de dermat. et syph. 29: 1686-1701 1933

popular and purpuric<sup>41</sup> or subcutaneous and nodular (Osler's nodes). They sometimes prefer the extensor surfaces sometimes the palms and soles (Janeway lesions).

These eruptions heal spontaneously. Petechiae on the rectal or sigmoid mucosa are supposed to be an early diagnostic sign in subacute bacterial endocarditis.<sup>42</sup>

### Rheumatic Fever

Rheumatic fever<sup>43 44 45</sup> is an infection probably caused by hemolytic streptococci. Hereditary and constitutional factors as well as exogenous factors like exposure to cold damp climate and youthful age favor the infection. The outbreak often starts with pharyngitis, tonsillitis and tender joints. Chills usher in the fever which is high but does not follow as regular a pattern as in



Fig. 8.—Rheumatic nodules

scarlet fever. Acute arthritis involving one joint after the other is the center of the clinical picture. Endocarditis, anemia and more rarely pleurisy, linitis, chorea and encephalitis may appear. While the mortality in the early stages does not exceed 3 per cent,<sup>46</sup> the frequent cardiac damage plays an important part in the mortality in later life.

The pathologic findings are characterized by small widespread circumscribed granulomatous nodules which are most often found in the ventricular walls of the heart (Aschoff bodies) and in the walls of many arteries especially of the aorta and the coronary and in the periarticular tissues.

LEHMANN, E. and SACKS, B. A Hitherto Undescribed Form of Valvular and Mural Endocarditis, *Arch. Int. Med.* 53: 701, 1933.

<sup>41</sup>FRISCH, J. I. (cutaneous) Petechiae as Diagnostic Sign in Subacute Endocarditis. *Internat. Clin.* 2: 27-27, 1941.

<sup>42</sup>LEICHTENSTRAIT, B. Acute Articular Rheumatism, in FLEISCHLER and SCHLOMMEYER, *Diseases of Children*, Vol. III, Philadelphia, 1934, J. B. Lippincott Company, pp. 373-378.

<sup>43</sup>LEICHTENSTRAIT, B. Die rheumatische Infektion im Kindesalter. *Klin. u. exp. Med. Kinderh.* 27: 1-29, 1930.

**Dermadromes**—The skin participates in the syndrome in various ways. *Pallor* is common. The skin of the extremities frequently becomes glossy and there may be redness of the palmar eminences. The palms are moist. The repeated sweating often causes miliaria, especially on the chest and the inner surfaces of the arms. *Peteckias* and other hemorrhagic signs have often been observed. Keil<sup>16</sup> saw them in 10 per cent of 523 cases. Recently<sup>17</sup> it has been demonstrated that children with rheumatic fever generally show a low capillary resistance, especially in late winter and before barometric depressions.



Fig. 9—Otan-subcutaneous rheumatic nodules about the olecranon.

*Urticaria* occurs in the early stages.<sup>18</sup> *Erythema nodosum* has often been linked to acute articular rheumatism,<sup>19-21</sup> but the evidence is scant and there is a modern tendency to deny any relationship.<sup>22</sup> The observation that such recognized rheumatic diseases as endocarditis and chorea are seldom connected with erythema nodosum has been interpreted as evidence against its rheumatic character.<sup>23</sup> (Kassowitz after Leichtentritt<sup>24</sup>)

<sup>16</sup>Keil, H. Rheumatic Erythemas, Ann Int Med 11 2246, 1933.

<sup>17</sup>Brown, E. E. and Wasson V. P. Capillary Resistance in Rheumatic Children, J. Pediat 19: 323-334 1941.

<sup>18</sup>Traub, Erich. Ueber die Bedeutung der Hauterscheinungen beim akuten Gelenkrheumatismus, Zechr f Kinderh 88 789-799 1937.

<sup>19</sup>Hadley H. H. Dermataes of Rheumatic Fever Urol. & Otan. Rev 48 713-714, 1941.

<sup>20</sup>Keil, H. H. Relation of Erythema Nodosum and Rheumatic Fever Ann I t. Med. 10 1680, 1937.

<sup>21</sup>Feer, E. Zur Aetiologie des Erythema nodosum Schweiz. med. Wchnsche 86 643-645 1915.

*Erythema multiforme*<sup>10, 11</sup> sometimes appears with exacerbations of the articular disease.

The erythemas in rheumatic fever seem to have been over-classified from a morphological viewpoint. It is sufficient to distinguish between nodular papular and erythematous rheumatic skin manifestations. Transitional forms exist. Keil<sup>12</sup> found 181 eruptions among 523 cases of rheumatic disease. Besides more or less nonspecific dermatoses like hemorrhagic eruptions, telangiectases urticaria scarlatiniform exanthems, in approximately 10 per cent of the cases rheumatic erythemas and in 7 per cent subcutaneous nodules could be found. *Erythema nodosum* is not included.



Fig. 10.—Cutaneous rheumatic nodules. (From Rosenberg, W. A. : Arch. Dermat., 1934.)

The *rheumatic nodules* (*rheumatismus nodosus*) appear in crops more often in the subcutaneous tissues than in the cutis itself.<sup>13</sup> They vary from mustard seed to olive size. They are movable nontender and covered with normal skin. They are most often found over the olecranon about the elbow joint, over the knuckles and other bony eminences, for example over the forehead and along the crest of the vertebrae. The nodules are often symmetrically distributed particularly on the limbs. The rheumatic nodules must be regarded as indicating activity of the rheumatic infection which means an unfavorable prognosis.<sup>14, 17, 18</sup> Other rheumatic lesions especially rheumatic heart disease are almost always

<sup>10</sup>Stange, O. Die Hautveränderungen beim akuten Gelenkrheumatismus, nebst Bemerkungen über Erythema multiforme. Wien klin. Wochenschr. 10: 841-844 1907.

<sup>11</sup>Ueber Theodor. Ein erythematöses-bullöses-pustulöses Exanthem bei Polyarthritide acuta, Dermat. Ztschr. 62: 308-374 1931.

<sup>12</sup>Meyer August. Ak. ter Gelenkrheumatismus mit Erythema pustulosum, Ztschr. f. klin. Med. 117 413-424, 1931.

<sup>13</sup>Reboul, J. Girard, J. and Fieard, D. U cas d'érythème multiforme au cours de la maladie de Desfiland, Bull. Soc. franç. de dermat. et syph. (Réunion dermat., Nancy) 48 1790-1793 1933.

<sup>14</sup>Rosenberg, W. A. Cutaneous Rheumatic Nodules, Arch. Dermat. & Syph. 30 377-384 1934.

<sup>15</sup>Struthers, R. R. and Racial, H. L. Significance of Rheumatic Nodules in Childhood, Canad. J. A. J. 40 378-381 1912.

present and the mortality is as high as 31 per cent.<sup>107</sup> Recently less pessimistic opinions on the prognostic significance of the rheumatic nodules have been voiced.<sup>108</sup> It has even been said that the appearance of rheumatic nodules may indicate the subsiding of the particular rheumatic incident though not of the disease.<sup>109</sup> Histologically they correspond to the Aschoff nodules of the myocardium. Leichtentritt<sup>110</sup> succeeded twice in isolating streptococcus viridans from excised nodules. In a third case he and Biberstein<sup>111</sup> found cocci in microscopic sections.

The rheumatic nodules must be interpreted as true infectious metastases. The rheumatic nodules usually heal occasionally they may take on the appearance of chronic, hard almond-sized subcutaneous cystic tumors in the neighborhood of the large joints especially the elbow. Such nodosities which are well known in other infectious diseases particularly spirochetoses are called juxta articular nodules.<sup>112</sup> H. Hoffmann<sup>113</sup> however in his comprehensive monograph on juxta articular nodes does not believe that rheumatic fever plays a part in the etiology of these lesions.

Cutaneous rheumatic nodules<sup>114</sup> are much rarer than subcutaneous ones. They have been observed on the fingers and palms as red not painful slightly indistinct papular lesions which do not ulcerate. They consist of perivascular infiltration with endothelial proliferation. In later stages giant cells develop.<sup>115</sup>

*Rheumatic papular erythema* is a discrete red eruption of small papules mainly but not exclusively about the articulations. Keil<sup>116</sup> found it in 3 per cent of his 523 patients with rheumatic fever. Like other rheumatic eruptions it appears in crops. Keil<sup>117</sup> separates erythema marginatum with polycyclic and raised borders from papular erythema. Much more significant and better known than the papular eruptions is the flat *annular erythema*<sup>118</sup> which is so characteristic and so intimately connected with rheumatic infection that it can be called a specific rheumatic dermatosis. The incidence given by various authors varies widely. Erythema annulare is still considered a rare complication which seldom occurs more frequently than in 10 per cent of children with rheumatic fever.<sup>1</sup> (Wallgren after Traub<sup>119</sup>) although Leichtentritt<sup>120</sup> and Lehdorff and Leiner<sup>121</sup> give figures higher than 60 per cent. These differences may be largely caused by the type of clinical material because erythema annulare is mainly a dermatome of rheumatic disease in children with endocarditis. The rash starts with pale bluish pink maculae of only a few millimeters in diameter. These spots soon blanch in the center and spread peripherally with an active but not infiltrated margin. Thus polycyclic or zigzag often rather than almost linear figures result.

<sup>107</sup>H. J. R. M. and Gibson, B. Rheumatic Nodules in Children, J.A.M.A. 119: 544-555 1912.

<sup>108</sup>McCulloch, H. in Discussion of Struthers, R. R., and Basal, H. L. Rheumatic Infection in Childhood. Sedimentation Rate and Schilling Count. Am. J. Dis. Child. 61: 1081 1930.

<sup>109</sup>Hopkins, H. H. Subcutaneous Nodules of the Juxta-Articular Type. Bull. Johns Hopkins Hosp. 49: 4-16 1931.

<sup>110</sup>Hoffmann, H. Juxtaartikuläre Knoten, Handb. d. H. u. Gk. 12, 1: 419-426 1932.

<sup>111</sup>Katz, O. Juxta-artikuläre Knoten bei Gelenkrheumatismus, Zeitschr. f. klin. Med. 129: 263 1930.

<sup>112</sup>Quadrat, J. Rheumatische Papulöse Erythema. Dermal Lesions of Aschoff-Kilgus Node Type. Case. Bull. de franç. d. dermat. et syph. 44: 1782-1783, 1931.

<sup>113</sup>Lehdorff, H. and Leiner, O. Erythema annulare. Ein typisches Exanthem bei Endokarditis, Zeitschr. f. Kinderh. 31: 40-53 1932.

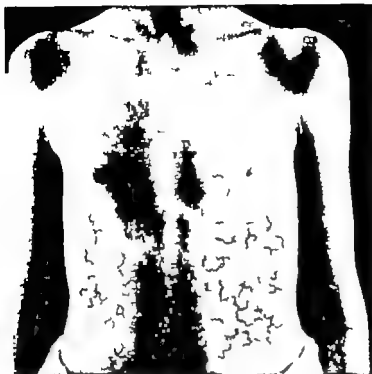


Fig. 11—Erythema annulare rheumaticum. (Courtesy Dr. Arthur F. Abt.)



Fig. 12—Erythema annulare rheumaticum. (Courtesy Dr. Erich Urbach.)

The lesions, which appear most often on the chest, less often on the abdomen back, and extensor surfaces of the limbs, are delicate, not infiltrated not scaly not tender and do not itch. The erythema has not been observed on the mucous membranes. It appears in one or several crops and the individual crops usually last two to five days.<sup>42</sup>

Since the eruptions may follow each other in short intervals the patient may have erythema for years. The rash may easily be overlooked. Leichtentritt<sup>43</sup> found erythema annulare always connected with rheumatic endocarditis or chorea and he emphasizes its ominous significance. Other authors do not share his pessimistic interpretation<sup>47,44</sup> but all agree that it has not been seen in endocarditis of nonrheumatic character.

The biopsy<sup>45</sup> shows neutrophilic infiltration as a main characteristic. Bacteria have not been found in the lesions. Löwenstein<sup>46</sup> and his group were able to cultivate the tubercle bacillus from the blood of one case of rheumatic fever with erythema annulare. This finding still lacks confirmation. The eruption is now regarded as an expression of cutaneous allergy.<sup>47</sup>

*Still's disease* is a chronic, articular disease of childhood. Fever, generalized lymphadenitis and splenic tumor are outstanding features. *Streptococcus viridans* has been demonstrated in the blood by Leichtentritt.<sup>48</sup> Periarticular papules and erythematous eruptions have been reported.<sup>49</sup>

*Paludromic rheumatism* is a disease characterized by often recurring relatively short attacks of arthritis.<sup>50</sup> Although there is no connection with rheumatic fever, intracutaneous and subcutaneous nodules mainly on the fingers have been described in some cases. The nodules were mostly short lived rarely persisting over a long period.

### Periarteritis Nodosa

Periarteritis nodosa<sup>51</sup> is characterized by multiple inflammatory destructive foci in the walls of the smaller arteries, which may lead to aneurysm and other severe circulatory disturbances. The clinical picture varies according to the area which is predominantly involved. Males outnumber females 3:1.<sup>52</sup> Age is not a decisive factor. Acute infectious diseases of many kinds have often been observed to precede the outbreak of periarteritis nodosa. The onset is usually though not always rapid. Repeated attacks and exacerbations often characterize

<sup>42</sup>Abt, A. F. Erythema Annulare Rheumaticum, Am. J. M. Sc. 190 634, 1924.

<sup>43</sup>Carol, W. L. L. and Van Krieken, J. A. Histopathologie des Erythema annulare von Lehnardt und Leiser, Acta paediat. 27 378, 1938.

<sup>44</sup>Löwenstein, Ernst. Die Tuberkelbacillämie in ihrer Auswirkung auf die Gesamtmedizin. Als einen klinischen Teil von Carl Reitter, Wilhelm Neumann und Otto Kren, Leipzig und Wien, 1936, Franz Deuticke.

<sup>45</sup>Urbach, H. and Bleier, A. Erythema Annulare Rheumaticum (Lehnardt Leiser). Case Arch. Dermat. & Syph. 41 515-530 1940.

<sup>46</sup>Jellisch, P. S. and Rosenberg, E. F. Paludromic Rheumatism, Proc. Staff Meet. Mayo Clin. 16 303-315, 1941.

<sup>47</sup>Kassanof, A. and Maier, R. Ueber eine bisher nicht beschriebene eigenartige Arterienkrankung (Periarteritis nodosa) die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellähmung einhergeht, Deutsches Arch. f. klin. Med. 1 454 1906.

<sup>48</sup>Harris, A. W. Lynch, G. W. and O'Hare, J. F. Periarteritis Nodosa, Arch. Int. Med. 62 1163-1183, 1939.

the course. In more than 90 per cent of the cases, the outcome is fatal after less than one year. In a review of 101 pathologically confirmed cases, Harris, Lynch and O'Hare<sup>120</sup> listed as significant symptoms and signs fever (80 per cent) leukopenia up to 5400 (70 per cent) renal manifestations like albuminuria (64 per cent) abdominal pain (27 per cent) cylindruria (46 per cent) hypertension (64 per cent) edema (52 per cent mostly of cardiac distribution) loss of weight, hematuria, and neuritis. Thoracic pain dyspnea headache and vertigo are common. The diagnosis is usually made post mortem. However with better knowledge of the dermatomes and greater number of biopsies the disease is being recognized more frequently during life.<sup>120,121,122</sup>

The cause of the disease is not known but it has nothing to do with syphilis as was early suggested. It is striking that periarteritis nodosa has so often developed shortly after or even in immediate connection with various infectious diseases especially those caused by hemolytic streptococci. While the staphylococcus, the meningococcus, and the gonococcus are on the list of bacteria which have been found in close association with periarteritis nodosa,<sup>123</sup> the streptococcus is by far the most frequent one. A correlation with rheumatic fever with Aschoff bodies and verrucous endocarditis was discovered in four of Spiegel's<sup>124</sup> seventeen cases and in one of Rothstein and Welt's.<sup>125</sup> The clinical course often suggests septicemia. The coincidence with well-established allergic states and also experimental evidence of infection<sup>126</sup> suggests allergy as an important pathogenic factor in periarteritis nodosa.<sup>127</sup>

The treatment is symptomatic. In one case sulfapyridine together with acetylcholine seemed to be curative.<sup>128</sup>

**Dermatomes.**—Cutaneous manifestations occur in about 25 per cent.<sup>122,129</sup> In rare instances almost exclusive involvement of the skin, without participation of the internal organs has been observed.<sup>130,131</sup> The case material permits a tentative grouping<sup>124,128</sup> into nodular erythematous, and hemorrhagic eruptions.

The most characteristic element is the periarteritic *nodule* which may be found in or under the skin. These nodules have been noted in roughly 25 per cent of the cases, but they probably often have escaped observation. The lesion is very seldom larger than a pea, more often smaller. In hemorrhagic cases the nodules may reach the size of a robin's egg<sup>132</sup> or larger and may become cystic and blood filled. The nodules which have been seen to appear in crops in various stages of the disease are hardly ever more than fifty in number. In order of frequency they have been observed on the forearm chest, legs, abdomen

<sup>120</sup>Vinberg, O. W. Periarteritis Nodosa, Arch. Dis. Childhood, 13: 31-44, 1938.

<sup>121</sup>Legros, J. Periarteritis Nodosa or Kussmaul-Mayer Disease. First Case Diagnosed in Infancy During Life. Recovery From Therapy With Sulfapyridine and Acetylcholine. Arch. Française de Pédiat., Paris, 2: 118-119, 1944-1945.

<sup>122</sup>Ketron, L. W. and Bernstein, J. O. Cutaneous Manifestations of Periarteritis Nodosa, Arch. Dermat. & Syph. 48: 820-844, 1936.

<sup>123</sup>Marras, A. Zur Kenntnis Form der Periarteritis nodosa, Wien. klin. Wchnschr. 51: 991, 1938.

<sup>124</sup>Spiegel, R. Periarteritis Nodosa, Arch. Int. Med. 58: 903, 1936.

<sup>125</sup>Dojdy, L. J. Periarteritis Nodosa, Cutaneous Symptoms, Bull. New York M. Coll., Flower & Fifth Ave. Hosp. 3: 175-182, 1940.

<sup>126</sup>Altshuler, J. Multiple nekrotisierende Periarteritis nodosa der Haut mit Aranthosis nigricans, Arch. f. Dermat. Syph. 158: 823, 1932.



The lesions which appear most often on the chest less often on the abdomen back, and extensor surfaces of the limbs, are delicate not infiltrated not scaly not tender and do not itch. The erythema has not been observed on the mucous membranes. It appears in one or several crops and the individual crops usually last two to five days.<sup>10</sup>

Since the eruptions may follow each other in short intervals the patient may have erythema for years. The rash may easily be overlooked. Leschtentritt<sup>11</sup> found erythema annulare always connected with rheumatic endocarditis or chorea and he emphasizes its ominous significance. Other authors do not share his pessimistic interpretation<sup>12,13</sup> but all agree that it has not been seen in endocarditis of nonrheumatic character.

The biopsy<sup>14</sup> shows neutrophilic infiltration as a main characteristic. Bacteria have not been found in the lesions. Löwenstein<sup>15</sup> and his group were able to cultivate the tubercle bacillus from the blood of one case of rheumatic fever with erythema annulare. This finding still lacks confirmation. The eruption is now regarded as an expression of cutaneous allergy.<sup>17</sup>

*Still's disease* is a chronic, articular disease of childhood. Fever generalized lymphadenitis, and splenic tumor are outstanding features. *Streptococcus viridans* has been demonstrated in the blood by Leichtentritt.<sup>16</sup> Periarthritic papules and erythematous eruptions have been reported.<sup>18</sup>

*Palindromic rheumatism* is a disease characterized by often recurring relatively short attacks of arthritis.<sup>19</sup> Although there is no connection with rheumatic fever intracutaneous and subcutaneous nodules, mainly on the fingers have been described in some cases. The nodules were mostly short lived rarely persisting over a long period.

### Periarteritis Nodosa

Periarteritis nodosa<sup>20</sup> is characterized by multiple inflammatory destructive foci in the walls of the smaller arteries, which may lead to aneurysm and other severe circulatory disturbances. The clinical picture varies according to the area which is predominantly involved. Males outnumber females 3:1.<sup>21</sup> Age is not a decisive factor. Acute infectious diseases of many kinds have often been observed to precede the outbreak of periarteritis nodosa. The onset is usually though not always, rapid. Repeated attacks and exacerbations often characterize

<sup>10</sup>Mabe A. F. Erythema Annulare Rheumaticum. Am. J. M. Sc. 190: 824, 1935.

<sup>11</sup>Carol, W. L. L. and Van Krieken, J. A. Histopathologie des Erythema annulare von Lehdorff und Leiber. Acta paediat. 17: 373, 1936.

<sup>12</sup>Löwenstein, Ernst. Die Tuberkelbacillen in ihrer Auswirkung auf die Gesamtschicksale. Mit einem klinischen Teil von Carl Reitter. Wilhelm Neumann und Otto Kres, Leipzig und Wien, 1936, Franz Deuticke.

<sup>13</sup>Urbach, E. and Hieser A. Erythema Annulare Rheumaticum (Lehdorff Leiber). Oss. Arch. Dermat. & Syph. 41: 515-520, 1940.

<sup>14</sup>Hirsch, P. A. and Rosenberg, E. F. Palindromic Rheumatism, Proc. Staff. Meet. Mayo Clin. 11: 806-818, 1941.

<sup>15</sup>Kussmaul A. and Mieser R. Ueber eine bisher nicht beschriebene akutgumliche Arterienkrankung (Periarteritis nodosa) die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskeldünung einhergeht. Deutsches Arch. f. klin. Med. 1: 484, 1908.

<sup>16</sup>Harris A. W. Lynch, C. W. and O'Hare J. P. Periarteritis Nodosa, Arch. Int. Med. 63: 1162-1182, 1939.

the course. In more than 90 per cent of the cases the outcome is fatal after less than one year. In a review of 101 pathologically confirmed cases Harris Lynch and O'Hare<sup>129</sup> listed as significant symptoms and signs fever (80 per cent) leukopenia up to 5400 (70 per cent) renal manifestations like albuminuria (64 per cent) abdominal pain (27 per cent) cylindruria (46 per cent) hypertension (64 per cent) edema (52 per cent, mostly of cardiac distribution) loss of weight, hematuria, and neuritis. Thoracic pain dyspnea headache and vertigo are common. The diagnosis is usually made post mortem. However with better knowledge of the dermatomes and greater number of biopsies the disease is being recognized more frequently during life.<sup>130,131,132</sup>

The cause of the disease is not known but it has nothing to do with syphilis as was early suggested. It is striking that periarteritis nodosa has so often developed shortly after or even in immediate connection with various infectious diseases especially those caused by hemolytic streptococci. While the staphylococcus the meningococcus, and the gonococcus are on the list of bacteria which have been found in close association with periarteritis nodosa,<sup>133</sup> the streptococcus is by far the most frequent one. A correlation to rheumatic fever with Aschoff bodies and verrucous endocarditis was discovered in four of Spiegel's<sup>134</sup> seventeen cases and in one of Rothstein and Welt's.<sup>135</sup> The clinical course often suggests septicemia. The coincidence with well-established allergic states and also experimental evidence of infection<sup>134</sup> suggests allergy as an important pathogenic factor in periarteritis nodosa.<sup>136</sup>

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<sup>129</sup>Harris, O. W. Periarteritis Nodosa. Arch. Dis. Childhood, 19 31-44, 1922.

<sup>130</sup>Legros, J. Periarteritis Nodosa or Kussmaul-Maior Disease. First Case Diagnosed in Infant During Life. Recovery From Therapy With Sulfapyridine and Acetylcholine. Arch. Française de Pédiat., Paris, 3 113-115, 1944-1945.

<sup>131</sup>Ketron, L. W. and Bernstein, J. O. Cutaneous Manifestations of Periarteritis Nodosa. Arch. Dermat. & Syph. 46 929-944, 1936.

<sup>132</sup>Jaurea, A. Zur kutanen Form der Periarteritis nodosa. Wien. klin. Wochenschr. 51 881, 1933.

<sup>133</sup>Spiegel, R. Periarteritis Nodosa. Arch. Int. Med. 58 903 1936.

<sup>134</sup>Doyd, L. J. Periarteritis Nodosa, Cutaneous Symptoms. Bull. New York M. Coll. Flower & Fifth Ave. Hosp. 8 175-182, 1946.

<sup>135</sup>Allerweire, J. Multiple nekrotisierende Periarteritis nodosa der Haut mit Acetylcholin-therapie. Arch. f. Dermat. Syph. 100 322 1933.

face back fingers, scalp scrotum and tongue.<sup>126</sup> Sometimes a linear reticular or livedo racemosa like arrangement and pulsation indicate their connection with an artery.<sup>127,128,129</sup> This connection can be demonstrated better by capillaroscopy (Weigeldt after Boyd<sup>130</sup>). The lesions are tender even painful and may be slightly raised purplish or red and surrounded by erythematous halos which may coalesce. The center may appear grayish and depressed indicating necrotic changes<sup>131</sup> and a scab may appear on superficial nodules. The nodular cases may suggest erythema nodosum.<sup>132</sup> The nodules have a tendency to heal leaving a tan-colored pigmentation. Matras believes that the nodular type of periarteritis nodosa takes a more benign course.

The second important cutaneous feature of the disease is *purpura*. Petechiae and small purpuric spots, sometimes with a white center<sup>133</sup> are common sometimes abundant. Large cutaneous extravasations (apoplexia cutanea)<sup>134,135,136</sup> resembling purpura fulminans have been described by many authors.<sup>137</sup> These hemorrhages may involve entire regions. They may break down and form gangrenous ulcers of varying sizes depth and numbers<sup>138,139</sup> sometimes climaxing in the mutilation of the acra of the extremities.<sup>140,141</sup> The coagulation time may be prolonged and the fibrinogen reduced to 50 per cent.<sup>142</sup>

Besides the most characteristic features the nodules the gangrene roseola<sup>143</sup> and other erythemas and ephemeral rashes mentioned. Pigmentation though not in the list compiled by Hare<sup>144</sup> is a feature and may have the characteristics of Addison's disease. Periarteritic involvement of the adrenals has in fact been reported in a few cases. (Spiegel after Boyd<sup>145</sup>). Edema and profuse sweating at night and moderate adenopathy are common symptoms.

The *histological* picture is well established. It shows infiltration of the walls of small and medium-sized arteries with leukocytes and round cells of the Langhans type are common. All layers especially the intima are thickened and the elastica and the muscle fibers are destroyed. Due to the proliferation of the intima leads to occlusion thrombosis, and hemorrhage. Age of the tissue and blood eosinophilia are frequently a conspicuous feature. There has been some discussion as to whether cutaneous fat is often the site of a patchy necrosis and of an inflammatory infiltration with necrosis in spots and numerous monocytes and giant cells. Extravasations are exceedingly common.

<sup>126</sup> Carol W. L. L. and Prakken, J. R. Periarteritis Nodosa, Acta dermat. venerol. 18: 102 1937

<sup>127</sup> Goldschlag, F. and von Chwalibogowski, A. Ueber einen Fall von Periarteritis nodosa mit verbreiteten Hauterschütterungen Arch. f. Dermat. Syph. 171: 622 1934

<sup>128</sup> Freund, P. Periarteritis Nodosa, Arch. Dermat. & Syph. 182: 158, 1920

<sup>129</sup> Lohr, H. and Rosenfeld, H. Multiple Hautgangrän bei Periarteritis nodosa, Dermat. Ztschr. 61: 299-330 1931

<sup>130</sup> Danowitch, M. M. Polayes, S. H. and Charot, R. Periarteritis Nodosa, Ann. N. Y. Acad. Sci. 14: 1149-1179 1942

<sup>131</sup> Rothbarth, J. L. and Welt, S. Periarteritis Nodosa, Am. J. Dis. Child. 48: 1277 1933

<sup>132</sup> Rich, A. R. and Gregory, J. E. Periarteritis Nodosa as a Manifestation of Hypersensitivity, Bull. Johns Hopkins Hosp. 72: 65 1943

<sup>133</sup> Moschcowitz, E. Periarteritis Nodosa, J. Mt. Sinai Hosp. 8: 237-239 1934

## Scarlet Fever

Scarlet fever is caused by certain strains of hemolytic streptococci which are found mainly in the discharges of the upper respiratory tract. Contagion occurs predominantly among children from 1 to 5 years of age (rarely in infants) by close contact with patients and possibly though seldom through carriers or media such as milk toys, or pets. The disease is most contagious during the first week. The incubation period is probably two days<sup>127</sup> but the observations vary from one to seven or more days. The onset is sudden with nausea and high temperature. A few convulsions and vomiting are common at this time but chills are uncommon. There are regularly early sore throat and a coated tongue. The scarlet fever exanthem appears after twelve to twenty four hours and reaches its height within five days, the patient frequently being very ill. The fever gradually falls, the rash fades and peels within three weeks and then recovery is reached unless complications develop. These complications include otitis media (14 per cent) arthritis (7 per cent) nephritis (4 per cent) and a number of rarer conditions (Hunt after Dick<sup>128</sup>).

The mortality<sup>127</sup> in the United States is between 1 and 2 per cent in some communities much less; this rate varies considerably during epidemics and in different countries. However approximately 4 000 deaths from scarlet fever occur every year in the United States. Except for the complications the post mortem findings are essentially negative. The diagnosis rests on the clinical picture especially the rash in connection with exposure, an epidemic, and the occurrence of hemolytic streptococci.

**Dermadromes.**—In rare cases, the outbreak of the disease may be preceded by a transitory diffuse or spotted rash on the inner thighs.<sup>129</sup> Such *fore-exanthems* occur in other exanthematic infections too. Most of the new monographs on scarlet fever do not mention this rash.

The scarlet fever *exanthem* appears early, often during the first day of the disease but occasionally the rash is delayed as much as five days.<sup>130</sup> Diffuse erythema of the palate with red spots<sup>130</sup> marks the appearance of the exanthem. This exanthem is quickly followed by the skin eruption which starting at the neck creeps downward and reaches the feet in two to three days. The face usually remains free but it is flushed from fever. Morawetz<sup>130</sup> mentions that the exanthem involves the face. The area around the mouth stays pale with a yellow hue. This diffuse and relatively wide circumoral pallor includes the lips and often the chin. It is much wider and less sharply limited than the narrow perioral strip which often remains unaffected in various other inflammations and pigmentations about the mouth. The rash is often particularly pronounced on the femoral triangles on the abdomen and in the bends of the joints. Here the folds may appear more marked and slightly hemorrhagic (Pastia's lines).

<sup>127</sup>Dick, G. F. and Dick, G. H. *Scarlet Fever* Chicago, 1938. The Year Book Publishers, Inc.  
<sup>128</sup>Toohey, J. A. *Scarlet Fever* in J. Breckenmann. *Practical Pediatrics*, Hagerstown, Md.

1944. W. F. Prior Company Inc.

<sup>129</sup>Schlesman, A. and Hottelinger, A. *Scarlet Fever* in Flanssler and Schlesman, *The Diseases of Children*, Vol. III, Philadelphia, 1938. J. B. Lippincott Company pp. 78-109.

<sup>130</sup>Morawetz, O. *Acute Exanthema Scharlach* Handb. d. H. u. Gk. 24: 418-424 1930.

The rash is a bright red erythema in which small punctate splashes can be discerned. On the extremities, the pin point spots are less numerous and therefore better recognizable. These very small points are engorged papillae<sup>133</sup> and follicles.<sup>133,144-145</sup> The swelling of the follicles and a slight infiltration of many of the red points may give a chagreen like impression to the hand. Mottling of the skin may be present on the extremities.<sup>144</sup> In unusual instances the skin is edematous making the rash look like dermatitis. Minute, clear rarely pustular<sup>146</sup> vesicles may be scattered over the red background. This phenomenon which is evidence of a more severe inflammation is known as *millaria scarlatiosa*. The vesicles the content of



Fig. 12.—Scarlet fever. Rash flushed face, and circumoral pallor on third day. (Courtesy Dr. Max Fox.)

which is alkaline do not correspond to the sweat glands. They may be abundant or even confluent forming large bullae.<sup>139</sup> The erythema fades on transient pressure or when the skin is stroked with the fingernail and after ten to twenty seconds a white sometimes slightly icteric dermographism appears.<sup>21</sup> Small numbers of *petechias* are common especially in the flexures. The tourniquet test is usually positive and petechiae can easily be provoked by pinching. Edema of the dermis often causes slight puffiness of the face, ears and fingers. The

<sup>133</sup>Ullrich, P. G. Histopathologie d. Hautkrankheiten, Berlin, 1904. A. Hirschwald.

<sup>134</sup>Kritch, N. Pachine, A. and Sidorow, P. La peau dans la scarlatine. Etud. histologique. Arch. de Méd. et nat. 32 313-326 1920.

<sup>135</sup>Oyon, Hermann, F. Scarlet Fever. Review of Literature. Med. Klin. 27 661-664 1941.

<sup>136</sup>Lehmann, W. Streptokokkenkrankungen. Ergebnisse d. inn. Med., Kinderk. 69: 604-749 1931.

<sup>137</sup>Sobel, N. La Mackee, G. M. and Cipollaro, A. O. Skin Diseases in Children, New York, 1946, Paul B. Hoeber Inc.

<sup>138</sup>Leibmann, E. J. *Millaria scarlatiosa* suppurativa, Med. Klin. 33 1358, 1937.

exanthem reaches its full height during the second half of the first week. It then disappears, often in the same order in which it came. During the period of involution the redness may still be pronounced in the evening although the skin appears pale in the morning. During the second week the skin becomes dry and the *desquamation* starts usually about the neck or on the lips sometimes at the sides of the face, showing that in these cases the scarlet exanthem had involved the face also. The desquamation is at first branny but in the third week the typical peeling in large flakes develops. The thick horny layers of the epidermis of the hands and feet are the last to go. The desquamation varies according to the intensity of the exanthem. While desquamation of fairly large shreds from the finger tips and toes is common the shedding of glove-like casts is quite rare. The epidermis which is ready to peel usually starts to crack under the toes and then peels off toward the tips as well as toward the soles. After a few days ragged flakes hang around the nails which in rare instances may come off also. It has often been said that the stripping of the shreds proximally from the nails over the digits is an almost diagnostic sign of preceding scarlet fever.



Fig. 11.—Scarlet fever. Desquamation.

Usually the exanthem does not itch. However the period of desquamation may be troubled by pruritus. Some cases of scarlet fever with a mild exanthem but unusually severe pruritus have been reported.<sup>46</sup> In rare cases the rash may fail to develop or may be very light. These cases are contagious and desquamation may or may not follow.

In true relapses of scarlet fever the exanthem may repeat itself<sup>47, 48</sup> however true relapses are exceedingly rare. *Desquamation erythema* or erythema post

<sup>46</sup>Lerici-Jacob L. Le prurit dans la scarlatine. La forme prurigineuse de la scarlatine, *Presse med.* 2: 267-269 1929.

<sup>47</sup>Hübneruck, Eberhard. Zur Klinik der Spätexantheme nach Scharlach, *Monatschr. f. Kinderh.* 69: 117 1933.

<sup>48</sup>Leiser, Carl. Hautveränderungen bei späteren Erkrankungen des Kindesalters, *Wien. med. Wochenschr.* 79: 1136 1929.

scarlatinum is a dermatosis which is seen in less than 1 per cent<sup>147</sup> during the desquamation period or during relapses. In one type there are round or polygonal red slightly papular spots of fingernail size or smaller which have an accentuated deep red margin and a collar of scales. They cover the lower trunk, the buttocks and the thighs in a much less regular or pronounced pattern than the exanthem.<sup>148</sup> Another variety is a cracked net-shaped erythema and dermatitis with desquamation.<sup>147</sup>

*Striae cutis distensae* are not infrequently seen in adolescent girls after scarlet fever (see striae in chapters on puberty and pregnancy)

Moderate swelling of the superficial *lymphatic nodes* is common during the eruption. The nodes under the angles of the jaws which correspond to the tonsils are often infected. These and other neck nodes rarely other lymphatic glands may suppurate and break down.

The *oral* manifestations of scarlet fever are of great importance.<sup>14</sup> In the initial stage before the exanthem the pharynx is reddened and the tongue coated. The diffuse initial redness of the throat soon changes into the enanthem which consists of bright red or hemorrhagic points especially over the soft palate and the anterior pillars. The uvula and the hard palate are often left free and relatively pale. The tonsils become swollen early white exudate showing in the lacunae. The exudate may form diphtheroid membranes and necroses which may cover the entire tonsil. Ulceronecrotic lesions may even invade the tongue<sup>144</sup> and extend to the pillars and the soft palate.

The changing and characteristic appearance of the *tongue* has for more than a century been considered of great diagnostic importance but recently it has lost some of its import since typical scarlatinal glossitis occurs in only one-half of the cases, and may also be found in measles and German measles.<sup>15</sup> The first changes in the tongue often precede the exanthem in scarlet fever.<sup>14</sup> The early yellowish coating is soon pierced by the swollen red papillae fungiforms, producing the strawberry tongue. The edges and the tip of the tongue usually become free early so that a red V-shaped area results.

After about two days the yellow coating vanishes. On the fifth to eighth day the whole tongue is deep red and covered with raised papillae constituting the raspberry tongue.<sup>148</sup>

Since the first description by Lister in 1858 (Klan<sup>144</sup>) a great number of cases of acute symmetric *gangrene* of the skin in scarlet fever have become known sometimes under names such as gangrenous purpura purpura fulminans or disseminated skin gangrene.

Suddenly sometimes after a mild or moderately severe course of scarlet fever usually in or shortly after the third week but occasionally as late as nine months after the onset<sup>15</sup> patches of gangrene may appear on the skin often in a

<sup>147</sup>Trunk, J. D. *Scarlet Fever*. Chap. XXI. New York 1940. Oxford University Press.

<sup>148</sup>Bergery, J. Ulcero-nécrotische Glossitis bei Scharlach. *Monatsschr. f. Kinderh.* 38: 229 1923.

<sup>149</sup>Céjan, N. J. État de la langue dans le scarlatine au moment de l'éruption. *J. de méd. de Paris* 40: 292-294 1921.

<sup>150</sup>Klan, H. Ak. asymmetrische Haut gangrän bei Scharlach. *Klin. Wchschr.* 18: 1623, 1927.

<sup>151</sup>Dick, G. F. Miller, E. M. and Edmundson, H. Gangrene in Scarlet Fever. *Am. J. Dis. Child.* 47: 274 1923.



Fig. 15.



Fig. 16

Fig. 15.—Scarlet fever tongue on third day. Coating is pierced by swollen papillae fungiformes. "Strawberry tongue." (Courtesy Dr. Max Fox.)

Fig. 16.—Scarlet fever fourth to fifth day. Tongue is swollen, desquamated along the edges. (Courtesy Dr. Max Fox.)



Fig. 17



Fig.

Fig. 17.—Scarlet fever fifth day. Tongue is clean on the area facing the soft palate. (Courtesy Dr. Max Fox.)

Fig. 18.—Scarlet fever between fifth and eighth days. Tongue is red, studded with swollen papillae. Raspberry tongue. (Courtesy Dr. M. Fox.)



symmetrical distribution. They occur most frequently on the legs, the buttocks, and the genitalia<sup>14</sup> occasionally on the arms, hands, face and chest.<sup>15</sup> They range in size from small patches to that of a whole region such as an entire foot or hand. The involved skin undergoes the well known sequence of changes of gangrene—pain, erythema, dark discoloration, blistering and finally demarca-



Fig. 18.



Fig. 20. E

Fig. 18—Patches of gangrene after scarlet fever. *Erysipela gangrenosum*. (Courtesy Dr. Max Fox.)

Fig. 20—Foot gangrene after scarlet fever. (Courtesy Dr. Max Fox.)

tion and slough. The hemorrhagic discoloration is not evidence of a hemorrhagic diathesis. The healing tendency is often surprising. The outcome depends upon the size of the lesions, the necessity for amputation, and the presence of other complications. The mortality is probably lower than 50 per cent.<sup>16</sup>

Wittber H.:  
Praxis 8: 5-11 1937  
Schäfer H. E.  
27 1919 1933

Kin Del rag sur Gangrän bei Erysipel im frühen Kindesalter. Kinderärztl.

Multiple Gangrene of the Skin Following Scarlet Fever. Arch. Dermat. & Syph.

The cause of this multiple symmetric gangrene is still little understood. Purpura capillary thrombosis and thrombophlebitis<sup>136</sup> have in several instances been shown not to be causative. Purpura has occasionally been present.<sup>137 138</sup> The findings in amputated limbs failed to demonstrate arterial block,<sup>133 139</sup> and the findings of phlebitis were more suggestive of a sequel than of a cause. Possibly the explanation may be found in allergic phenomena. Gangrene has often been observed during the third or fourth week, the typical time of post-scarlatinal nephritis and has actually been seen together with it.

Another rare complication of scarlet fever is *thrombophlebitis migrans*. This is an acute febrile phlebitis usually involving the veins of both legs.<sup>136 140</sup>

*Circumscribed edema* is another rare sequel of scarlet fever.<sup>141</sup> It has been known for a long time but it is apparently seen only in some epidemics. Steinbrinck<sup>142</sup> reported forty cases of edema of the upper lids in a recent epidemic. The swelling was in some instances so severe that it suggested subluxation of the eyeball. Involvement of the paranasal sinuses probably plays a part. All the skin changes discussed under the heading of septicemia may be observed occasionally.

*Purpura* though relatively rare in scarlet fever may occur just as in the course of other infections. It has been seen most often during the third week. The platelet count may be normal<sup>143</sup> or low. The mortality is high.<sup>144</sup> Hemorrhagic tendencies can be demonstrated early.

The *tourniquet test* is commonly positive in scarlet fever in fact it had been devised first as a diagnostic procedure in scarlet fever.<sup>145</sup> Lately the capillary resistance has been investigated by E. E. Brown<sup>146</sup> with the more exact Dalldorf<sup>147</sup> suction method. It can be shown that the capillary resistance as expressed by the number of petechiae provoked under certain conditions is low at the onset and increases as the patient recovers. Age of the patient,<sup>148</sup> toxemia, and marked desquamation may lower the resistance.<sup>149</sup> Myrberg<sup>150</sup> saw wavelike recurrences of lowered resistance in intervals of about two weeks. He<sup>151</sup> demonstrated that

<sup>136</sup>Hilsewerna, E. J. and Silverstein, D. M. Postscarlatinal Phlebitis. *Am J Dis Child*, 29 447 1933.

<sup>137</sup>Box, Ch. R. and Birmingham, R. Purpura Hemorrhagica Complicating Scarlet Fever. *Lancet* 1 295-296, 1931.

<sup>138</sup>Wendt, Odd. Purpura mit Ausschlag der Hautkrose bei richtiger Scarlatina, *Norsk Med L Lægevidensk* 25: 14-16, 1931.

<sup>139</sup>Urbach, Erick, and Gottlieb, Philip M. *Allergy* New York, 1943. Grune & Stratton, Inc.

<sup>140</sup>Barnes, J. V. Postscarlatinal Thrombophlebitis Migrans. *Brit M J* 1 645, 1943.

<sup>141</sup>Kochinsky H. Eine ungewöhnliche Form von Gefäßveränderung beim Scharlach. *München med Wchnschr* 84 1900 1936.

<sup>142</sup>Steinbrinck, W. Unusual Complications (Scarlet Fever). *Deutsche med Wchnschr* 63 1 1143-50 1943.

<sup>143</sup>Fox, M. J. and Knorr, N. Consideration of Phenomenon of Purpura Following Scarlet Fever. *Am J M Sc* 194 851 1934.

<sup>144</sup>Wood-Smith, F. G. Purpura as Complication of Scarlet Fever. *Brit J Child Dis* 28 373-281 1931.

<sup>145</sup>Leeds, E. Tourniquet Test in Scarlet Fever. *München, med Wchnschr* 58 293 1911.

<sup>146</sup>Brown, E. E. Scarlet Fever—Capillary Resistance. *Arch Pediat* 57 433-43 1940.

<sup>147</sup>Dalldorf, O. A Criterion of Hemorrhagic Diathesis in Experimental Scary. *J Exper Med*, 53 229 1931.

<sup>148</sup>Myrberg, A. Capillary Resistance and Wheal Test in Scarlet Fever. *Upsala Medaf forh* 37 417-430 1932-33 48 197.

Fig. 21



Fig. 22

Fig. 21 —Severe purpura after scarlet fever (Courtesy Dr. Max Fox)

Fig. 22 —Severe purpura after scarlet fever (Courtesy Dr. Max Fox)

the absorption time of a saline wheal (McClure-Aldrich test<sup>109</sup>) is shortened especially in the beginning and in toxic cases.

*Capillaroscopy* shows, even in the early period, the capillaries to be lengthened and engorged on the arterial side. The subpapillary plexus is hyperemic and plainly visible on a brownish background. The arterial flushing yields later to a stasis with both sections of the capillaries about equally filled with cyanotic blood. It is more than five weeks until the capillaries appear bright red again on a rosy background with sharply outlined margins and a hardly discernible subpapillary plexus.<sup>110</sup>



Fig. 22.—Purpura after scarlet fever. (Courtesy Dr. Max Fox.)

The *Dick test* for susceptibility to scarlet fever is based on the neutralization of scarlet fever toxin in the skin of the person tested. Exactly 0.1 c.c. of the test solution is injected intracutaneously.<sup>111</sup> The test is considered positive if after twenty to twenty-four hours an erythema however slight of not less than 10 mm. in any diameter is present. The reading should be done in bright light. Induration is not required and may even be absent in strongly positive reactions. A positive reaction shows that the person is susceptible to scarlet fever. The test is usually negative in the newborn infants of immune mothers but becomes positive during the first year of life.

<sup>109</sup>McClure W. B. and Aldrich C. A. Time Required for Disappearance of Intracutaneously Injected Salt Solution. *J. A. M. A.* 81: 293-294, 1923.

<sup>110</sup>Müller-Otfried. *En Beobachtung des Capillarkreislaufs beim S. scarlet.* Verhandl. d. deutsch. Kong. f. innere Med. 23: 211-220, 1921.

The newborn infant of a nonimmune mother usually reacts positively. In later life the reaction depends on the degree of exposure and silent immunization. In a group of children who grow up in crowded conditions, for example in an



Fig. 24—Positive tourniquet test (Lorenz-R. model sign) in scarlet fever. (Courtesy Dr. Max Fox.)



Fig. 25—Positive blanching test in scarlet fever. (Courtesy Dr. Max Fox.)

institution the incidence of susceptibility may be as low as 10 per cent and in rural groups with few contacts it may be as high as 85 per cent.<sup>10</sup> The morbidity among children in Milwaukee with negative reactions to the Dick test was found to be only about one fourteenth of the general morbidity (Cummings after von Bormann<sup>11</sup>). Convalescents of scarlet fever have negative Dick tests.

<sup>10</sup> von Bormann F. *Scharlach*, Monatschr. f. Kinderh. 82: 212-261 1910.

In rare instances a mild miniature scarlet fever may follow the Dick test.<sup>173</sup>

The *blanching or Schultz-Charlton test*<sup>174</sup> (Auslöschphänomen) is based on the local blanching of the scarlet fever exanthem by an intracutaneous injection of normal serum serum of convalescent scarlet fever patients or serum of diluted antitoxin in amounts of 0.1 to 0.5 c.c. A positive reaction consists of blanching of the rash eighteen to twenty four hours after the injection in a zone surrounding the central red spot where the injection was made.<sup>175</sup> The positive Schultz-Charlton test<sup>176</sup> supports the diagnosis of scarlet fever. The area of skin which has been blanched does not peel.<sup>177</sup>

There is still controversy about the limitations of these two tests.<sup>178, 179</sup>

**Pathology**—There is edema, hyperemia and inflammatory infiltration especially around the follicles and sweat glands. Endothelium-covered fibrous exudates have been seen in the walls of small veins in scarlet fever as well as in other pyogenic infections,<sup>177</sup> especially subacute bacterial endocarditis. Parakeratosis precedes the peeling.<sup>180</sup>

It is remarkable that hemolytic streptococci are common in the superficial scales of the peeling skin but could rarely be found in the deeper layers.<sup>181</sup> This may mean that the scales become infected from without, and that the living skin during the desquamation is no longer infected. Recently streptococci have been demonstrated in the endothelial cells of blood and lymphatic capillaries and in adjacent cells.<sup>182</sup> The desquamated skin is not considered contagious.<sup>184</sup>

<sup>173</sup>Walls, H. B. Miniature Scarlet Fever After Dick Test, *Lancet* 2: 219 1946.

<sup>174</sup>Schultz, W. and Charlton, W. Serologische Beobachtungen am Scharlachexanthem, *Ztschr. f. Kinderh.* 17: 322-323 1916.

<sup>175</sup>Fanconi, G. Beiträge zum Scharlachproblem, Abhandlungen aus der Kinderheilkunde und ihren Grenzgebieten, N. 11 Berlin, 1930, S. Karger.

<sup>176</sup>Reisman, H. A. and Berkow, A. Dick Test, *Arch. Pediat.* 58: 230-25, 6-11.

<sup>177</sup>Press, H., and Litvak, A. M. Schultz-Charlton and Dick Test in Scarlet Fever *Arch. Pediat.* 58: 194-197 1941.

<sup>178</sup>Magnusson, H. Oeflervandreaktionen, *Verhandl. d. deutsch. path. Gesellsch.* 29: 261 1935.

<sup>179</sup>Kanavskaya, M. J. Presence of Streptococci in Scales of Scarlet Fever Patients, *J. A. M. A.* 89: 1011, 1927.

<sup>180</sup>Torack, J. E. Etiology and Pathogenesis of Scarlet Fever. Histologically Demonstrated Storage of Oocyst-like Structures in Endothelial Cells of Skin, Mucous Membrane and Lymph Nodes, *Klin. Wochschr.* 21: 581 1943.

## CHAPTER III

### SYSTEMIC INFECTIONS

#### Lobar Pneumonia

In none of the various types of lobar pneumonia are skin manifestations important with the exception of *herpes simplex* (herpes febrilis herpes symptomaticus) which occurs in a high percentage, between the second and fifth day usually on the lips. The eruption appears as groups of clear vesicles on a red slightly edematous base. After one to two days the vesicles become pustular often confluent and finally they dry up. The crusts come off after about five days usually without leaving a scar. The incidence of herpes varies according to the type of pneumococcus. Among 500 cases of lobar pneumonia of all types 30 per cent were herpetic.<sup>109</sup> This incidence was observed in London, England. The herpes incidence among 500 cases in New York was only 12 per cent,<sup>110</sup> while many older mostly German figures run as high as 40 or even 50 per cent. J. A. Montgomery<sup>111</sup> analyzed the occurrence of herpes in 500 cases of lobar pneumonia with regard to types of pneumococci. While the incidence of herpes is about the same (30 per cent) in all types the mortality in the herpetic is lower than in the nonherpetic cases, especially in type I in which the mortality is less than one-sixth of that of the nonherpetic of the same group. The relatively favorable prognosis of herpetic pneumonia has been well established<sup>112-114</sup> for a long time. Montgomery<sup>111</sup> records a mortality of 14 per cent in the herpetic group and 16 per cent in the total. Schwartz's<sup>115</sup> corresponding figures are 5 and 25 per cent which is closer to the old figures.<sup>116</sup>

Herpes is uncommon in acute Friedländer pneumonia which has a high mortality (75 per cent).<sup>117</sup>

*Petechias* occur in severe cases of pneumococcal sepsis. E. Fraenkel<sup>118</sup> examined such lesions in two fatal cases. Clinically they seemed to be only petechiae the histological structure suggested bacillary metastases but no pneumococci could be found. E. Fraenkel<sup>118</sup> emphasizes the rarity of skin manifestations in pneumococcal infections. He believes that the skin enjoys a certain immunity to pneumococci since skin metastases are lacking even when specific metastases are found in many other organs.

<sup>109</sup>Montgomery J. A. Herpes febrilis in Lobar Pneumonia. *Lancet* 1 1041 1042, 1929.

<sup>110</sup>Schwartz J. Pneumonia. 500 Cases. *M. Rec.* 147 19-200 1933.

<sup>111</sup>Schönfeld W. Die klinische Bedeutung des Herpes simplex für andere Krankheiten und physiologische Zustände. *Tsune-Chi med. Monatsschr.* 52: 295-302 1937.

<sup>112</sup>Yarrell O. Herpes Simplex. *München med. Wochenschr.* 83 339-344 1936.

<sup>113</sup>Goodall H. Life-Story of Simple Herpes. *Lancet* 1 906 1939.

<sup>114</sup>McLennan H. Chronic Friedländer Infection of the Lungs. *J. A. M. A.* 118 1827 1828, 1940.

<sup>115</sup>Fraenkel E. Metastatische Dermatosen bei akuter bakterieller Allgemeinerkrankung. *Ztschr. f. Hyg. u. Infektionskrankh.* 76 163 1914.

Equally rare are diffuse or maculovesicular *erythemas*<sup>187 188</sup> A few times, pneumococci have been found in the skin lesions. The rare varicella resembling rashes may be generalized herpes.<sup>189</sup>

As long as the fever is high the skin remains hot and dry. It is an old observation that the *cheek on the side of the involved lung is redder* than the other. The most plausible explanation is that the patient often lies on the involved side in order to keep this painful side quiet but this explanation is not always correct.<sup>187</sup> Only during and after the crisis do profuse sweats occur especially in juveniles. These sweats are sometimes followed by miliaria rubra.

# Systemic Pyocyanus Infection

In spite of the common infection of wounds with *Pseudomonas aeruginosa* (*Bacillus pyocyanus*) and of the frequent saprophytism of this microorganism systemic infection is rare and occurs usually in debilitated persons.<sup>190 191 192</sup> Almost all organs may become infected the skin often being involved. The skin manifestations of severe pyocyanus sepsis do not differ from those of other pyemia. However there is a characteristic dermatosis *ecchyma gangrenosum* which is known to occur in the wake of measles and various other infections and cachectic states (see Fig. 19) especially in children and which in a considerable number of instances has been shown to be caused by *Pseudomonas aeruginosa*. Its character as a skin manifestation of a generalized infection is shown by many analogous autopsy findings in internal organs.<sup>193</sup> The skin lesions start as papules, but soon become bullous and hemorrhagic and form round sharply outlined necrotic and painful ulcers which may reach the subcutaneous tissues and even invade the muscles. Petechiae and large ecchymoses are supposed to be characteristic.<sup>194</sup> Their number varies from one lesion to exanthematic dissemination. Healing has seldom been observed since most of these patients die within a short time. The general course is that of a septic toxemia.<sup>195</sup>

The histologic examination shows many gram-negative bacilli in the outer layer of the blood vessels especially of the arteries.<sup>196</sup> Atypical apparently hematogenous skin infections with pyocyanus have occasionally been described.<sup>197 198</sup>

# Meningococcal Meningitis (Cerebrospinal Fever)

After an incubation period of a few days the onset is usually sudden with high fever severe headache, and vomiting. Meningitic symptoms ap-

<sup>187</sup>Hewar C P and Mills E S. *Parasitica*, Oxford Monographs, Vol. X. New York 1929, Oxford University Press.

<sup>188</sup>Chenik-Labasse F and Ot C. *Zur Klinik, Histologie und Pathogenese der Pneumokokkeninfektion*. Arch f Dermat. Syph. 189: 431-438, 1923.

<sup>189</sup>Sharpe Wm S. Eruption Resembling Varicella in Lobar Pneumonia. Brit. M. J. 1: 14, 1923.

<sup>190</sup>Frank, O. Die Pyocyaneosekrankungen der Haut. Handb. d. H. Gk. 9: 1: 125-144, 1929.

<sup>191</sup>Klose H S and Aeschl A R. Three Fatal Cases of Bacillus Pyocyanus Infection. J. A. M. A. 82: 822-823, 1923.

<sup>192</sup>Levandosky F. Ulceröse Hautaffektion bei Erwachsenen, verursacht durch d. Bacillus pyocyanus. Mischow med. Wchnsch. 1907 II: 2273.

<sup>193</sup>Fret, W. and Wiener K. Ein Fall von ulceröser Hauterkrankung aus der Gruppe des Ecchyma gangrenosum (mit Pyocyaneusebefund). Arch. f. Dermat. Syph. 124: 100-118, 1921.



pear after from two to four days. There is irregularity of the pulse and respiration painful stiffness of the muscles abolition of superficial abdominal reflexes, insomnia and restlessness. The patient lies on his side with the knees drawn up. The leukocytosis may be very high.

After the first week the patient's restlessness often changes to stupor. The recovery is gradual the course is varying death may occur in any stage.

Before the advent of the sulfonamides the mortality rate was as high as 49 per cent in children under the age of one year and from 10 to 20 per cent above this age.<sup>134</sup> Today the mortality rate has been lowered to 2 per cent<sup>135</sup> and even less.<sup>136</sup>

The sulfonamides and penicillin are the drugs of choice in the treatment of meningococcal infections.

**Dermadromes.**—A variety of rashes occur with varying incidence. Figures between 91<sup>37</sup> and 100 per cent<sup>138</sup> are available.<sup>139</sup>



Fig 26.—Meningococcal meningitis. Purpuric rash. (Courtesy Dr. M. Fox.)

Of importance is a *purpuric rash* consisting sometimes of only a few petechiae occasionally of very many hemorrhagic spots resembling flea bites or larger. The rash often being scanty one should look for purpuric lesions on the chest armpits, abdomen thighs buttocks and hips. A single petechia of the conjunctiva may

<sup>134</sup>Wroster Drought C. and Kennedy A. M. Cerebro-spinal Fever. London, 1919. A. & C. Black Ltd.

<sup>135</sup>Thomas H. M. J. Meningococcal Meningitis and Septicemia. J. A. M. A. 122: 264-272, 1942.

<sup>136</sup>Hill, L. W. and Lever H. S. Meningococcal Infection in an Army Camp. J. A. M. A. 122: 9-14, 1942.

<sup>137</sup>Blackerby P. F. and Oandil F. W. Epidemiologic Study of Approximately 400 Cases of Cerebrospinal Meningitis. Comparative Value of A Rhinix and Antibacterial Serum. South. M. J. 21: 181-185, 1925.

<sup>138</sup>Dickson, R. C. M. Kinnon, N. E. Magner H. and McElherry N. D. Meningococcal Infection. Lancet 1941 II: 621-624.

be the only lesion.<sup>130</sup> The purpuric rash may develop exceedingly rapidly almost under the eyes of the observer. There is no parallel between the extent of the rash and the severity of the infection<sup>130</sup> as had been thought by many older authors.<sup>131</sup> However purpura seems to be of more ominous significance than petechiae<sup>130</sup> and the fulminating purpura of the Waterhouse Friderichsen syndrome is an almost certain omen of a fatal outcome. Larger purpuric lesions may become vesicular, bullous or ulcerative. Petechiae are not restricted to the skin. They may appear in the conjunctivae, in the oral mucosa and in the serous membranes. The great significance of the purpuric rash lies in the fact that the



Fig. 27 — Meningococcic meningitis. Papulohemorrhagic rash. (Courtesy Dr. Max Fox.)

lesions are true *metastatic bacillary lesions* not hemorrhages due to lowered capillary resistance of toxic cause. E. Fraenkel<sup>132</sup> found meningococci in the cellular infiltrate of the petechial efflorescences. He also demonstrated Friedlander bacilli in the purpuric skin lesions of a case of meningitis caused by this microorganism. Since then the search for microorganisms in purpuric lesions has become a diagnostic method. Tompkins<sup>133</sup> and McLean and Caffey<sup>134</sup> were able to demonstrate diplococci in smears in 80 per cent of their cases. To obtain material for the smear a purpuric spot is gently blanched between two fingers and pricked with a fine hypodermic needle. Then some serum is squeezed out and

<sup>130</sup>Newcomer W. and Frazer E. M. Summary of 80 Cases of Cerebrospinal Fever. *U. S. N. M. Bull.* 41: 969-973 1943.

<sup>131</sup>Tompkins V. N. Diagnostic Value of Smears From Purpuric Lesions of Skin in Meningococcic Disease. *J. A. M. A.* 123: 31-33 1943.

<sup>132</sup>McLean E. and Caffey J. Endemic Purpuric Meningococcus Bacteremia in Early Life. The Diagnostic Value of Smears From Purpuric Lesions. *Am. J. Dis. Child.* 42: 1032-1074 1923.

Fig. 28.

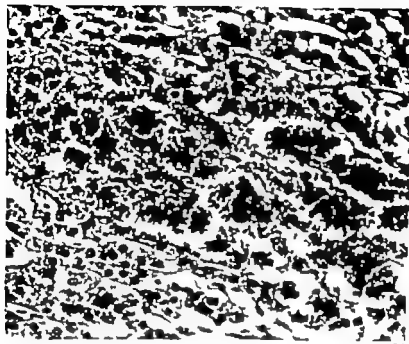


Fig. 29.

Fig. 28—Fulminating meningococcemia (Waterhouse-Friderichsen syndrome). Emorrhage of capillaries in zona fasciculata with early hemorrhagic extravasation. (From Pratt Thomas, Kelley and Gaze. *Bou h N J* 1945)

Fig. 29—Fulminating meningococcemia (Waterhouse-Friderichsen syndrome). Meningococci in polymorphonuclear leukocytes in smear from purpuric lesion (Gram stain, X2000). (From Pratt Thomas, Kelley and Gaze. *Bou h N J* 1945)

placed on a slide. Quantity is not an object but it is important that the prick be superficial and the exudate not diluted by peripheral blood. The smear is stained with Giemsa or Wright stain. The smears taken from lesions other than purpuric ones are usually negative.

The second type of cutaneous manifestation in meningococcic infection is a *maculopapular rash* which is sometimes seen as early as on the first day of illness. It is described as consisting of discrete slightly palpable rather



Fig. 30.—Purpuric lesions in meningococcic meningitis. (Courtesy Dr. Max Fox.)

scanty (rarely more than a dozen) inconspicuous, round well-defined pink spots of from 5 to 35 mm in diameter.<sup>1040</sup> The eruption may coincide with or closely follow the onset or a recurrence of the fever and the general symptoms of the infection.<sup>1041</sup> The lesions are most often found on the trunk and along the extremities especially about the shoulders. They are tender do not appear in crops and vanish within about four days. Sometimes they become purpuric in the center and palpable like erythema nodosum. Only rarely have they a morbilliform character but they often resemble the rose spots of typhoid fever to such a degree that all other diagnostic factors must be considered in order to avoid errors. An early appearance especially on the extremities seems to indicate meningitis rather than typhoid. During epidemics this rash alone is considered characteristic enough to establish the diagnosis of meningococcic septicemia.

<sup>1040</sup>Herrick, W. W. *Meningococcus Infections*. Oxford Medicine Vol. I New York, 1940 Oxford University Press, pp. 71-106.

<sup>1041</sup>Tyler, R. 204 Cases of Cerebrospinal Fever. *J. Roy. Army M. Corps* 78: 249-250, 1911.

Several *other types of cutaneous lesions* have been described. They include transient rubelliform<sup>244</sup> or scarlatiniform erythematous rashes hemorrhagic vesicles hemorrhagic gangrene<sup>245</sup> and a peculiar urticaria consisting of a large wheal on the buttocks. The latter which has been seen by several authors was supposed to be a foreshadowing of a fatal outcome<sup>184</sup> in the pre-sulfa era. *Herpes* often extensive and in atypical distribution is present in about one-third of the cases. While often seen on the fourth day it may appear at any time after thirty-six hours from the onset.<sup>246</sup> *Herpes zoster* involving almost all of the known sites is conspicuously frequent as in lobar pneumonia. The vesicles may contain meningococci. The belief that herpes is a favorable sign was held by many of the earlier authors however this is not true. The opinion was probably caused by the relatively favorable prognosis of herpetic pneumonia.

### Gonorrhea

Gonorrhea is predominantly a disease of the mucous membranes. Cutaneous involvements are rare. Ulcerations of the genital skin folliculitis and abscesses or pseudoabscesses are mostly due to exogenous infection of epithelial ducts or follicles from the gonorrheic urethra. Hematogenous gonococcal infections of the skin can be grouped under *transitory* urticarial erythematous or hemorrhagic exanthems of the type seen in other bacteremias and *keratotic* eruptions which are characteristic of gonorrhea and hardly known in other diseases.

There is a great morphologic variety of exanthems in the former group which makes it difficult to correlate the rash with the gonorrhea by any other evidence than coexistence even after the possibility of an eruption from sandalwood oil cubebs and similar drugs used in gonorrhea has been ruled out. The eruptions which have been described have been seen not only in febrile septic cases but also in relatively mild infections. If they repeatedly come and go with exacerbations of the gonorrheic infection the connection is quite obvious. The best proof of the specific nature of the questioned eruption is of course the finding of gonococci in the skin lesions. This has been accomplished in several cases.<sup>247</sup> In one case of septicemia caused by gonococci a macular rash was seen together with arthritis and endocarditis.<sup>47</sup> Gonococci could be demonstrated in the blood in the endocardium and in the erythematous spots. Keri<sup>248</sup> saw simple erythema together with epididymitis. Scarlatiniform<sup>249</sup> urticarial eruptions with hemorrhagic tendencies occupying the lower legs<sup>21</sup> vesicular<sup>250</sup> vesiculohemorrhagic,<sup>251</sup>

<sup>244</sup>Stverth, rue N. and Cameron, O. Meningococcus Ifection, J. Pediat. 18: 618-627 1941

<sup>245</sup>Poisson, R. Claude, P. A. Basel, J. and de Balmann, A. Meningococcemic Gangrenous Pyopur Associated With Cerebrospinal Meningitis. Cure by Serotherapy Sulfadiazide and Vitamin A, Bull. et mém. Soc. méd. d. hôp. de Paris 58: 801-806 1939

<sup>246</sup>Margolin, E. S. Gonorrheal Dermatitis as Part of Systemic Gonorrhea, Urol. & Gynec. Rev. 47: 512-514 1943

<sup>247</sup>Dorner, L. Gonokokkenempfe, München med. Wchnschr. 79: 1060, 1923.

<sup>248</sup>K. H. W. Gonokokkenexanthem, Zbl. 49: 587 1925

<sup>249</sup>Cojau, G. Septicémie gonococcique récidivante: ves d'effarations rares, Rev. roum. d'Urol. 3: 495-502 1936 Zbl. 94: 346

<sup>250</sup>Sehivian, S. J. Cutaneous Eruptions Accompanying Gonorrhea. Case II Hemorrhagic E. anthem, Urol. & Gynec. Rev. 38: 93-95 1934

<sup>251</sup>Keil, H. Type I Gonococcal Bacteremia With Characteristic Hemorrhagic Vesiculo-Pustular and Bullous Skin Lesions, Quart. J. Med. 7: 118 1938



Of much greater dermatological interest are the rare *hyperkeratoses* in gonorrhea *keratoderma blennorrhagicum* (*keratosis blennorrhagica*). Only 166 cases have been described since Vidal's<sup>21</sup> first observations in 1893. It has been estimated that *keratosis blennorrhagica* occurs about once in 5,500 cases of gonorrhea.<sup>22</sup> These dermatoses form a clinical picture which is almost exclusively connected with gonorrhea and it certainly is one of the most characteristic dermatomes peculiar to any one infection. Most of the patients are young men suffering from chronic urethral gonorrhea, usually with complications particularly arthritis and ocular complications. The gonorrheal infection frequently is of long standing<sup>23</sup> even many years when the rash breaks out. The eruption often starts with a papuloveascular exanthem. In some cases the primary lesion is described as a small glossy pink papule resembling a droplet of wax. The vesicles dry up but instead of peeling as one would expect they transform into pseudopustular lesions which look yellow but do not contain pus. These become keratoses and finally form a large hobnail-shaped conical lesion of layer texture. The keratoses are rupoid limpet-shaped and have a flat or umbilicated top with a yellow center which contains brittle white horny detritus. The bottom layer of horny material forms a yellow clifflike ring around the lesion which is sometimes surrounded by an inflammatory areola. The keratotic top is easy to remove leaving a shallow pink slightly moist or gelatinous<sup>24</sup> erosion. Keratoses at these areas are often of follicular origin. The lesions may grow slowly from pinhead size to several centimeters in diameter and they may coalesce into large rough hyperkeratotic plaques mostly on the soles and around the big joints particularly if the joints are inflamed. In these plaques many pseudopustular cavities may be found. The extremities are in some cases studded with button or medallion-shaped lesions which may reach 1 cm in thickness. The penis is a site of predilection for the gonorrheic dermatomes<sup>25</sup> which may appear as typical keratotic papules. On the glans and on the inner surface of the foreskin they may appear as glossy red flat papules or macules<sup>26</sup> which may coalesce into polycyclic patches. Sometimes the keratotic character of these lesions is marked by a grayish macerated crumbling horny top layer (*balanitis circinata*). The *keratoderma* may even be restricted to such penile eruptions. These lesions occasionally resemble a syphilitic chancre (Tullien after Langer<sup>27</sup>) or lichen planus.

The scalp sometimes becomes involved<sup>28</sup>. The nails<sup>29-30</sup> often become thick dull and brittle and subungual keratoses may raise or loosen the nail. The

<sup>21</sup>Vidal, E. Eruption généralisée de croûtes cornées. *Verh. d. derm. u. syph. Ges.* 4: 3, 1893.

<sup>22</sup>Stroickinger, L. Quelques considérations sur la lésion blennorrhagique. *J. d. med.* 82: 251-257, 1931.

<sup>23</sup>Micholt, M. Gonorrheal Keratoderma. *Arch. Derm. & Syph.* 21: 961-968, 1930.

<sup>24</sup>Urbina and Meyer-Delius. *Gon. Hyperkeratos. Balanitis circinata gonorrheica retractiliter*. *Vorh. d. Derm. & Syph.* 100: 3-20, 1911.

<sup>25</sup>Karman, W. L. Blumenthal, F. and H. Idemreich, J. *Blennorrhagie Balaniforme Keratoderma*. *Arch. Derm. & Syph.* 39: 472-479, 1939.

<sup>26</sup>Frühskil. *Keratosis blennorrhagica*. *Zbl.* 81: 283, 1935.

<sup>27</sup>Cederberg, A. Abortivformen der gonorrheischen Keratodermien. *Act. dermat. venereol.* 13: 43-52, 1933.

<sup>28</sup>Cornbleet, T. and Pace, E. R. *Keratoderma Blennorrhagicum*. *Arch. Derm. & Syph.* 89: 291, 1934.

whole nail bed even the entire tips of the fingers or toes may be covered with the keratotic masses. In several instances sharply contoured round or poly cyclic irregular grayish patches with erythematous borders have been observed on the palate and on the buccal *mucosa*.<sup>222 227 228 229</sup>

The general *distribution* of the rash is largely symmetrical. All *degrees* of involvement from a single keratotic patch on the penis<sup>224</sup> to universal erythroderma have been seen. Naturally the discomfort and suffering of the patient depends on the extent and the degree of tenderness of the individual lesions. The appearance of new crops is usually coupled with renewed arthritic attacks. The eruption may last months or years depending mainly on the course of the gonorrhea but also on the degree of involvement of the skin. The majority of the cases of keratosis blennorrhagica finally heal but about 10 per cent fatal ties have been recorded.<sup>21 22</sup>

The *histological* picture is characterized by heavy keratosis and parakeratosis with formation of cavities. There are edema and cellular infiltration in the papillary stratum.

*Gonococci* have been found in typical lesions in at least seventeen instances<sup>223 226 228</sup> although much more often the efforts to find the microorganisms have been in vain. The positive findings are definite proof of the hematogenous infectious nature of the eruptions which already had been suggested by the clinical relationship to arthritis endogenous conjunctivitis and iritis and the symmetric and follicular distribution on the extremities. Occasional observations give further support to the conception of a focal infection. Scholtz<sup>221</sup> saw a flare-up of the joint symptoms, and the appearance of a new crop of heavily crusted lesions after 8 c.c. of gonorrheal vaccine (instead of 0.8 c.c.) had been administered by mistake. Similar reactions have been seen after treatment with vaccine<sup>221</sup> and warnings against vaccine therapy of such hyperergic patients have been voiced.<sup>227</sup> The extirpation of the infected seminal vesicles resulted in the healing of a gonorrheic exanthem and the dilatation of a urethral infiltration or other urethral manipulations produced flare-ups<sup>221</sup> in at least five instances<sup>222</sup> (Lewin after Langer<sup>225</sup>). These observations are not only evidence that the gonorrheic keratodermas are caused by focal infection but they show the role allergy plays in producing the characteristic clinical entity. The scarcity of the gonococcus has its analogy in the paucity of microbes in tuberculids trichophytids and other

<sup>222</sup>Frel, W. Gon. Exanthem der Mundschleimhaut, Balanitis circinata gonorrhoeica bei Ochronidiosis. *Sbl* 41 271 1923.

<sup>223</sup>Oale, Ed Driver. Keratoderma Blennorrhagica. *Arch Derm & Syph* 19: 426-437 1929.

<sup>224</sup>Barrett, C. O. Keratoderma Blennorrhagica: no cases Gonococcus in Local Lesions. *Arch Derm & Syph* 22: 627-628, 1930.

<sup>225</sup>Combes, F. O. and Dehrman, H. T. Use of Vitamin A in Keratosis Blennorrhagica. *Arch Derm & Syph* 40: 722-23, 1942.

<sup>226</sup>Kewenig, T. Keratoderma blennorrhagica. *Glas Ital di Dermat* 11: 24-26, 1931. *Sbl* 22: 242.

<sup>227</sup>Alberle H. Erythema gonorrhoeae exfolianses arthropathies multiples rosules tropiques. *J d mal cutan et syph* 1900. *Gaz méd Nantes* 1900.



ida. The complement fixation reaction has several times been found to be positive<sup>212-214</sup>

The provocation of specific lesions by irritation with phenol<sup>217</sup> (not confirmed by Keim<sup>218</sup>) by herpes lesions (Buschke after Langer<sup>219</sup> Gjesing after Langer<sup>220</sup>)



Fig. 22.—Keratoderma blennorrhagicum. Rheumatism gonorrhoicus. (From Lever W. F. and C. Ford, G. Marshall Arch. Dermat. 1944.)

by inoculation with gonococcal pus and by maceration with wet dressings<sup>221</sup> demonstrates the changed capacity to react which has developed under the influence of the infection. Possibly the blennorrhagic keratoses are caused by inoculation of gonococcal pus into an allergic skin which has acquired the peculiar keratogenic tendency.

<sup>217</sup>W. and Jacob. Keratoderma blennorrhagicum Arch. Dermat. & Syph. 21: 703-704, 1920.

<sup>218</sup>Lohe H. and Rosenfeld H. Klinische und pathologisch-chemische Untersuchungen über die Blennorrhoidenbildung bei Gonorrhoe und bei Psoriasis pustulosa arthropathica. Derm. Ztschr. 65: 355-374, 1929.

<sup>219</sup>Illerensen H. B. and Ebert M. H. Keratoderma blennorrhagicum Arch. Dermat. & Syph. 31: 738-741, 1925.

<sup>220</sup>Lever H. and Percival C. H. Keratoderma blennorrhagicum. Lancet 1922 II: 1118-1121.

<sup>221</sup>Katsuj. O. Sek. Infektionskrankheiten der Keratoderma Gonorrhoe. J. p. J. Derm. & Urol. 22: 89, 1922. Xb1: 63, 702.

<sup>222</sup>Kim H. L. Histogenesis of Keratoderma blennorrhagicum Arch. Dermat. & Syph. 9: 422, 1924.

<sup>223</sup>Lindner W. Ueber Keratodermien im Zusammenhang mit gonorrhoischen und blennorrhoiden. Pflügers Arch. dermat. exotol. 9: 227-234, 1927.

The predominance of the male sex in a ratio of 15:3:1<sup>22</sup> and some autopsy findings seem to support the assumption of endocrine influences.<sup>214,217</sup>

In a small number of clinically typical cases it has not been possible to secure the diagnosis of a gonorrheic infection<sup>218,219,220</sup> nor to obtain a suggestive history. In the cases with a history of gonorrhea even many years prior to the dermatosis the existence of gonorrhea can hardly be ruled out.



Fig. 23.—Reiter's disease. Lesions are first follicle pustules containing masses of epithelial cells, later hyperkeratotic. From Lever W. F. and Crawford G. Marshall: Arch. Dermat. 1944.

Lately several cases of the syndrome arthritis, urethritis, conjunctivitis and keratoderma have been described in which all efforts to corroborate gonorrheic infection failed.<sup>21, 221, 222</sup> These cases belong at least in part to *Reiter's disease*, the etiology of which is unknown. Penicillin is ineffective.

Widome and Jensen: Gonorrheic II perkeratosis ohne Gonorrhoe. *Acta* 32: 22.  
 Lever W. F. and Crawford G. M.: Keratotic Dermatoses Without Gonorrhea. *Reiter Disease*. Arch. Dermat. & Syph. 49: 290-297 19.  
 McFerguson A. G. and Le Frank J.: Keratoderma Blennorrhagica. Some Further Observations as to Etiology. Brit. J. Dermat. 55: 25-34.  
 Rosenberg J. C.: Reiter's syndrome. J. Urol. 64: 556 1945.

The similarity of gonorrheic keratosis to arthropathic psoriasis may be considerable. However the history and presence of psoriasis the vesicular primary lesions the degree of keratosis the distribution the gonorrheic evidence and a biopsy will secure the diagnosis. In psoriasis the arthritis follows the skin lesions while gonorrheal arthritis is more likely to precede the exanthema.<sup>341</sup> Rupoid or tertiary syphilis may have to be ruled out.



Fig. 35.—Reiter's disease. Keratotic road lesions on glass pins. (Courtesy Dr. Sargen.)

The treatment is to heal the gonorrheic infection. The treatment with vaccines should be undertaken with the greatest caution to prevent exacerbations. Many authors stress the importance of proper nutrition and nursing of these patients who are often extremely weak, uncomfortable, emaciated and anemic. Vitamin A had good effect in one case after sulfathiazole had failed.<sup>340</sup> As local measures salicylic acid in plasters and ointments to remove the excessive keratotic masses should be applied. Great care should be taken to avoid irritation and maceration of normal skin in order to prevent provocation of new keratoses. Penicillin has in the only reported case of its application in keratosis blennorrhagica<sup>342</sup> failed to influence the course. It must be given further trial with high doses and prolonged treatment.

### Poliomyelitis

Rashes are not a characteristic of infantile paralysis. Red dermographism (tache cérébrale) is mentioned.<sup>343</sup>

<sup>340</sup>Espelin, E. Differential Diagnosis of Keratosis Blennorrhagica and Psoriasis Arthropathica. Arch. Dermatol. & Syph. 48: 547-559, 1930.

<sup>341</sup>Estabrook, E. M. Keratoderma Blennorrhagicum, Am. J. Syph. Gonorr. & Ven. Dis. 29: 241, 1943.

<sup>342</sup>Wilson, J. L. Poliomyelitis, Oxford Medicine, vol. V, New York, 1940, Oxford University Press, pp. 107-124.

### Erysipelas

Singer<sup>16</sup> observed various simple polymorphous or purpuric erythemas in the course of 25 per cent of his erysipelas cases. No substantial confirmation of this observation has become known.

### Chancroid

Lennhoff<sup>17</sup> reported a case of erythema nodosum-like eruption in a case of *ulcus molle*. The secondary lesions ulcerated. Ducrey Unna bacilli and were inoculable into the normal skin of the patient. Werther<sup>18</sup> succeeded in demonstrating the streptobacillus in the blood in a case of disseminated *ulcus molle*. Hematogenous infection from a soft chancre seems to be exceedingly rare since hardly any other well-corroborated cases have become known.

### Typhoid Fever

Typhoid fever is an endemic and epidemic, contagious, food or water borne disease caused by a gram negative motile bacillus *Escherichia typhi*. After an incubation period of from one to two weeks the disease starts insidiously with a slowly rising fever which reaches a high level with small morning remissions during the second week and diminishes by lysis during the third week or later. The pulse is much slower than the temperature would lead one to expect.

Abdominal and splenic tenderness and diarrhea with pea-soup-like stools are the most common symptoms. Delirium and severe general emaciation are other clinical features at the height of the disease.

Complications in almost every organ are known and the severity of the disease varies from symptomless carriers and walking typhoid to fatal cases. The outstanding post mortem finding is hyperplasia of Peyer's patches in the small and large bowel. The hyperplasia often results in ulceration which may lead to hemorrhage perforation and peritonitis. The spleen is enlarged and there is fatty degeneration of the liver.

**Dermatomes.**—Typhoid fever has a characteristic exanthem known as *rare spots* or *roseola*. The rash consists of thin almost macular papules which blanch on pressure and measure hardly more than one-half centimeter in diameter. They appear in small crops and last about three to five days. While the crops come and go about one to two dozen lesions are usually present from the end of the first week of the disease to the second or third week, rarely outlasting the fever. They almost always disappear without desquamation or pigmentation. In rare instances the rose spots are papular<sup>19,20</sup> hemorrhagic, or vesicular.

<sup>16</sup>Lennhoff, K. Über einen Fall von krypten verbreiteten hämatogenen Metastasen an der Uteruswand bei welchem Chancroid. Arch f. Derm. Syph 191 80-84 1921

<sup>17</sup>Werther. Multiple disseminiert. Ulcera molle, bei welchem Streptobacillen aus dem Histe produziert, wurden. Zbl 87 723 1921

<sup>18</sup>Derr, E. Cutaneous Affections in Various Diseases. Brit J. Derm., 19: 430, 1906

<sup>19</sup>Rosenthal, N. K. Zur Kenntnis seltener Hauteruptionen bei typhöser Erkrankung. Dermat. Wchnschr 89 861-863 1929

The eruption is mostly concentrated on the abdomen the chest and the back, and it usually appears first on these areas. Only in exceptionally dense eruptions does it invade the limbs and then the density decreases distally. The neck is rarely involved and the face remains free.<sup>301</sup> The exanthem is a scanty one compared with those of other infections particularly in small children. The number of rose spots seems to vary in epidemics. An abundant rash is no indication of the severity of the infection.<sup>301,302</sup> While some good observers failed to detect the exanthem in as high as 20 per cent,<sup>302</sup> other authors (Eichorst after Miller<sup>303</sup>) were able to detect rose spots in all the 2 000 cases of a series.

The *pathological* examination of the lesion shows a superficial rather than mainly leukocytic perivascular infiltrate in the upper corium which in the rare papular lesions invades the epidermis.<sup>37,303,303,304</sup> The lack of plasma cells is striking.<sup>304</sup> Typhoid bacilli are in rare instances seen as metastatic deposits in the lymphatic spaces or between the cuts and the epidermis<sup>304</sup> which may become separated within the small area of the rose spots. Frequently they can be cultured from the rose spots. However with the development of the blood culture this method has lost its diagnostic importance.<sup>305</sup>

*Hemorrhagic exanthems* in typhoid are rare. H. Curschmann<sup>301</sup> saw only 6 among 2 000 cases (all six patients died). The percentage was higher in other epidemics (McCrae after Miller<sup>306</sup>). Curschmann's<sup>301</sup> observation of a small epidemic of typhoid with purpura is remarkable. A mother and six children all showed purpuric rashes. While their cases took a favorable course the father developed a hemorrhagic bullous eruption and died.<sup>306</sup> Röper<sup>307</sup> saw a similar case with extreme thrombopenia and leukopenia. The bullae appeared especially over the bony prominences.

Scarlatiniform morbilliform papular<sup>308</sup> varioliform<sup>304</sup> and other rashes may occur<sup>308</sup> (Da Costa after Dore<sup>309</sup>) but they are rare. The absence of herpes is notable. Osler<sup>310</sup> saw herpes only 20 times in 1,500 cases. Several clinicians feel that the presence of herpes should be a warning against a premature diagnosis of typhoid fever.

*Miliaria crystallina* (sudamina) is supposed to be more common than in other infections. The content of the clear vesicles is neutral or slightly acid. The blisters dry up and are destroyed before they become pustular. Miliaria appears mainly on the abdomen the chest and the thighs, not on the face.<sup>301</sup> Urticaria is an occasional (0.3 per cent) complication. *Furunculosis* and *decubitus*

<sup>301</sup>Curschmann, H. Der Typhus abdominalis in Noronagel. *Speziell. Pathologie und Therapie*, vol. III Vienna, 1903, Alfred Hölder pp. 103-118.

<sup>302</sup>Miller J. L. Typhoid Fever. Oxford Medicine vol. IV New York 1940 Oxford University Press pp. 656-734.

<sup>303</sup>Poehlmann, A. Urtens an Typhus und Paratyphusroseolen. *Arch. f. Dermat. u. Syph.* 121: 231-252, 1921.

<sup>304</sup>Frankel E. Roseola typhosa und paratyphosa, München med. Wchnschr. 9: 323-327, 1916.

<sup>305</sup>Baerlekin, K. Abdominal Typhus, Kofke und Wassermann. *Handbuch der pathogenen Mikroorganismen* vol. III 2 p. 1214, 1931.

<sup>306</sup>Röper K. Bullose hämorrhagische Dermatosen bei Typhus, München med. Wchnschr. 2: 2020-2027, 1931.

<sup>307</sup>Truesdell B. Typhus abdominalis mit atypischem Exanthem, München med. Wchnschr. 73: 2249-2250, 1920.

<sup>308</sup>Gottschalk O. Variolartiges Inflixexanthem bei Typhus abdominalis, München. med. Wchnschr. 72: 17, 1925.

are common and troublesome. Curschmann<sup>201</sup> described a type of bed sore which he often saw as a subcutaneous decubitus. Subcutaneous abscesses developed in the pressure areas and later opened forming multiple sinuses. Both furunculosis and decubitus can to a certain extent, be prevented by meticulous nursing care. Mottled sallowlike pigmentation and depigmentation has often been seen on the abdomen of children after typhoid fever.<sup>202</sup>

*Noma* and other buccal ulcerations are very rare complications. Other ulcerations include *ulcus vulvae acutum*<sup>203,204</sup> and a annular vulvar ulceration<sup>205</sup> with raised edges and a necrotic floor.

The tongue is furred especially at the height of the disease. The edges and the tip are often clean in contrast to the dorsum.

The face is flushed in the early period and dull and listless later.<sup>206</sup> Osler and Christian<sup>207</sup> emphasize the yellow color of the palms and soles and mention a very distinctive musty odor of the skin. The author has been unable to find more exact observations on this odor and in attending many patients with typhoid he has been unable to notice it.

*Effluvium capillorum* is very common after typhoid but only rarely does it reach extreme degrees with complete loss of the hair. *Beau's lines* of the nails are usually noticeable but shedding of the nails is rare.

The diagnosis of typhoid fever cannot rest upon the roseola alone but it constitutes a most valuable diagnostic criterion. For most practical purposes the paucity of the lesions, the complete blanching on pressure, the distribution on the trunk and especially the abdomen and the appearance of recurring crops will suffice to distinguish the roseola in typhoid from the rash in spotted typhus and other rickettsial diseases. In the rickettsioses the more abundant rash appears within two days in one outbreak, is usually hemorrhagic, and the individual lesion is less neat and regular. There is more tendency to involve the extremities especially the more distal parts.<sup>208</sup>

A negative Wassermann and lack of other syphilitic manifestations will rule out syphilitic roseola which is usually abundant and has larger individual lesions.

### Paratyphoid Fever

The clinical picture in paratyphoid fever including the rash resembles typhoid fever. The rash was seen in about one-half of the cases of an epidemic recently observed in England.<sup>209</sup>

The *rose spots* in paratyphoid are more numerous than in typhoid. They occasionally cover even the hands and cheeks and desquamation occurs. Like the rose spots in typhoid fever the roseolae of paratyphoid are true bacterial

<sup>201</sup>Henné, Vaa. J. Hauterkrankungen bei dem infantilen Abdominaltyphus, *Oberst. Spital* 21, Hahner, Special Lese 23-24 1904 Bd 51 22

<sup>202</sup>Berlin, O. Ulcus vulvae acutum in Typhoid Fever. *Arch. Dermat. & Syph.* 22: 69-81 1922

<sup>203</sup>Zanacchi, P. Ulcerazioni specifiche del genitali esterni di una malattia di febbre tifoidale. *Ped. Clinica* (sez. prat.) 45 1637 166 937

<sup>204</sup>Johnson, B. and Battey, P. Typhoid With Buccal Ulcerations and Terminal Hemorrhoids in Child. *Years Old*. *Marquette* 2: 602-608 1919

<sup>205</sup>Fraser, W. M. Oloffe, B. T. J. and Glass, V. Epidemic of Paratyphoid B Fever in Liverpool and District. *Brit. M. J.* 2: 360-371 1927

metastases which contain bacilli sometimes even when the blood culture fails to demonstrate them. The pathology of the inflammatory reaction is similar to that of typhoid<sup>364</sup>

### Brucellosis (Undulant Fever)

Brucellosis (undulant fever) is a mild septicemia caused by bacteria of the genus *Brucella* which includes several pathogenic varieties. *Brucella melitensis* (Bruce) is found in goats, *Brucella abortus* (Bang) in cattle and *Brucella suis* (Traum) in swine. The microorganisms are very small pleomorphic, gram negative nonmotile bacteria which are pathogenic for guinea pigs. The infection from goats is also known as Mediterranean or Malta fever the infection from cattle as Bang's disease.

The routes of infection in man are the gastrointestinal tract and the skin. The incubation period varies from ten days to three weeks.<sup>365</sup> The onset is gradual and the course of the fever varies. Most characteristic is the undulant type with repeated periods of persistently high temperature of ten to twenty days in duration. The general condition remains good the paucity of objective signs is a remarkable clinical feature<sup>366-367</sup>

The disease is rarely fatal but a great number of complications are known. They include heart and lung manifestations, arthritis neuritis meningitis encephalitis orchitis mastitis abortion and others. The laboratory diagnosis is based on agglutination blood cultures which need two weeks to grow and skin tests with brucella vaccines which are more reliable than serum agglutination<sup>368</sup>. The cutaneous reactions can be used for differentiation of the various types.

**Dermadromes**—Skin manifestations are either ectogenous or hematogenous. The former occur at the site of contact with infectious material particularly on the hands and forearms of veterinarians after delivery or manual removal of the placenta of Bang infected cows. These persons, as a rule do not have a general Bang infection. They seem to become silently sensitized by repeated contacts. Thirty per cent of 325 Danish veterinarians<sup>369</sup> 10 per cent of the Swiss<sup>70</sup> and 20 per cent of fifty veterinarians from Michigan<sup>371</sup> suffered from this allergy. In some cases warmth or itching and urticaria are felt during or very shortly after the contact. While this early reaction may be caused by other substances in the cattle serum or placenta<sup>367 372</sup> a second type of eruption a

<sup>364</sup>Frankel E. Ueber Bosnische paratyphosen, Zeitschr f Hy Infektionsk 33 373-374, 1921

<sup>365</sup>Hardy A V Jordan, O F and Bortz, I R. Undulant Fever Nat l vt Health Bull N 135 pp 80 1931

<sup>366</sup>R. bloom F H and Evans A O. Chronic Brucellosis, J A M A 113 301-306 1936

<sup>367</sup>Hodderison J F. Brucellosis in Man and Animals, New York, 1943 Commonwealth Publ

<sup>368</sup>Hodderison J F. The Diagnosis and Control of Brucellosis, J Oklahoma M A 35 106-111

1942

<sup>369</sup>Hartmann, H and Thomsen, A. Brucella-Ansteckung bei Tierärzten. Ein charakteristische professionnelle Hautaffektion wahrscheinlich allergischer Natur hervorgerufen von Bacillus abortus (Bang) Arch f Dermat & Syph 123 477-491 1931

<sup>370</sup>McClellan A. Skin Lesions in Brucellosis. Praxis 32 551-561, 1913

<sup>371</sup>Hodderison J F and Johnson, H W. Brucellosis I. The Significance of Brucella Abortusline

in the Blood of Veterinarians, J A M A 84 1905-1907 1930

<sup>372</sup>Jadassohn, W. Brucella-Dunst-Ansteckung und Urticaria bei Tierärzten. Zbl 94 320

papulopustular folliculitis which develops within two days, is generally considered to be a specific reaction to *Brucella abortus* (Bang). The eruption is described by Huddleson<sup>267</sup> as consisting of small discrete elevated, reddish widely separated follicular papules from 2 to 5 mm in diameter and 1 to 2 mm in elevation. The rash itches or burns intensely and may last as long as three or four weeks. Occasionally deep necrotic tuberculid-like lesions or erythema exudativum multiforme-resembling forms are seen. Erythema brucei<sup>268</sup> as the condition has been termed by Huddleson and Johnson<sup>271</sup> is rarely followed by general brucellosis (Dieterl and others after W. Jadassohn<sup>272</sup>). In some of the sensitized persons the attacks seem to become more acute with renewed exposures.<sup>273</sup>

The systemic infection infrequently (11 per cent<sup>274</sup>) produces rashes. Their incidence seems to differ in various countries. They have been described as macular as resembling the roseola in typhoid<sup>275,276,277</sup> (Curschmann after W. Jadassohn) as star-shaped vividly red or purple spots on the forearms neck and face in porcine cases<sup>278</sup> morbilliform<sup>279</sup> scarlatiniform<sup>280</sup> (Grocco after Lustig and Vernoni) erythema exudativum multiforme-like,<sup>281</sup> as papular rashes involving cheeks, neck and extensor surfaces,<sup>282</sup> hemorrhagic bullous<sup>283</sup> varicelliform<sup>284</sup> and as resembling dermatitis herpetiformis and lasting over three years.<sup>285</sup> The appearance in crops and the evanescent character of the rash are often emphasized. Aphthae in the mouth and a bad taste are sometimes noted early. Tonsillitis vesiculosa and uvulitis have been described.<sup>286</sup> Ulcus vulvae acutum occurs as a complication as it does in typhoid fever.<sup>287</sup>

Gabb<sup>287</sup> tried to differentiate the dermatomes of morbus Bruce (Malta fever) and morbus Bang. In the former he found the rash more often scarlatiniform. Profuse and exhausting sweats are one of the most unpleasant features of brucellosis.<sup>287</sup> Sudamina, maceration and desquamation often follow the sweats.<sup>288</sup>

1. I was almost so rashes have been observed in a large number of cases. (Personal communication to the author from Dr. Borts and Dr. Jordan, Des Moines, Iowa.)
- 267 Huddleson R. Brucella-Ausschlag bei Typhoiden. *Medber. Zbl.* 88: 342, 1922.
- 268 Huddleson R. Bang-Infektion des Menschen. *Eryth. d. Hya. Bakt. Immunolog. Abstr.* Therap. 12: 443-448, 1923.
- 269 Kirschnering J. Bang's Disease in Man. *Stecher f. Biol. Fortsch.* 18: 440-442, 1922.
- 270 Löffler W. Frühe und späte Bang des Menschen. *Leipzig*, 1920. Carl Kohnen.
- 271 Lustig W. Übertragung der Banginfektion vom Schwein auf den Menschen. *Schw. med. Wochenschr.* 61: 970-972, 1921.
- 272 Kirschnering J. Bang's Disease in Man. *Stecher f. Biol. Fortsch.* 18: 440-442, 1922.
- 273 Kirschnering J. Bang's Disease in Man. *Stecher f. Biol. Fortsch.* 18: 440-442, 1922.
- 274 Kirschnering J. Bang's Disease in Man. *Stecher f. Biol. Fortsch.* 18: 440-442, 1922.
- 275 Kirschnering J. Bang's Disease in Man. *Stecher f. Biol. Fortsch.* 18: 440-442, 1922.
- 276 Kirschnering J. Bang's Disease in Man. *Stecher f. Biol. Fortsch.* 18: 440-442, 1922.
- 277 Kirschnering J. Bang's Disease in Man. *Stecher f. Biol. Fortsch.* 18: 440-442, 1922.
- 278 Kirschnering J. Bang's Disease in Man. *Stecher f. Biol. Fortsch.* 18: 440-442, 1922.
- 279 Kirschnering J. Bang's Disease in Man. *Stecher f. Biol. Fortsch.* 18: 440-442, 1922.
- 280 Kirschnering J. Bang's Disease in Man. *Stecher f. Biol. Fortsch.* 18: 440-442, 1922.
- 281 Kirschnering J. Bang's Disease in Man. *Stecher f. Biol. Fortsch.* 18: 440-442, 1922.
- 282 Kirschnering J. Bang's Disease in Man. *Stecher f. Biol. Fortsch.* 18: 440-442, 1922.
- 283 Kirschnering J. Bang's Disease in Man. *Stecher f. Biol. Fortsch.* 18: 440-442, 1922.
- 284 Kirschnering J. Bang's Disease in Man. *Stecher f. Biol. Fortsch.* 18: 440-442, 1922.
- 285 Kirschnering J. Bang's Disease in Man. *Stecher f. Biol. Fortsch.* 18: 440-442, 1922.
- 286 Kirschnering J. Bang's Disease in Man. *Stecher f. Biol. Fortsch.* 18: 440-442, 1922.
- 287 Kirschnering J. Bang's Disease in Man. *Stecher f. Biol. Fortsch.* 18: 440-442, 1922.
- 288 Kirschnering J. Bang's Disease in Man. *Stecher f. Biol. Fortsch.* 18: 440-442, 1922.



Only few histological examinations of the lesions have been made and they refer to the contact eruptions or to cutaneous reactions with *Brucella melitensis* allergen. Perifollicular and perivascular infiltration with lymphocytes leukocytes, and monocytes and occasionally an abscess have been observed <sup>272-273, 282</sup>

### Plague

In bubonic plague the primary skin lesion is caused by the bite of an infected rat flea. It may remain small and painless or it may develop into a pustule or even into a carbuncle followed by large suppurating bubos and septicemia. In the pulmonary form of plague a rapidly fatal septicemia follows or accompanies the severe pneumonia. The exciting organism is *Pasteurella pestis* which is found in the blood the sputum the urine and in many lesions especially in the bubonic pus. No other bacillus is known to occur in bubos in such large numbers.<sup>28</sup>

The disease is prevalent among several rodents. Occasional cases or small epidemics have often been seen in the western and southern United States. The data on the mortality and the value of serum and other treatment are extremely divergent. In many epidemics the mortality was higher than 80 per cent.

**Dermadromes.**—Hemorrhagic inflammation is a characteristic feature of the infection. This is particularly true of the *plague carbuncle* which otherwise does not differ very much from any other carbuncle. The plague carbuncle starts as a small infiltrate with one or several blisters on its surface. These blisters may coalesce into a bulla with seropurulent and often hemorrhagic contents in which plague bacilli abound. The bleb disappears fast, leaving a deep necrotic ulcer with raised edges on top of a rapidly growing cellulitis. A lymphangitic streak, sometimes with bubonuli connects the carbuncle with the regional lymph nodes which turn into *bubos*. The development of the carbuncle may become arrested in any stage leaving hard cutaneous infiltrates which abound in bacilli and are known as *plague boils*.

The plague carbuncle is only occasionally the primary lesion of the plague infection. More often the carbuncle is a metastatic, hematogenous or lymphogenous infection.<sup>29</sup> Sometimes the carbuncle develops at the site of infection at a later time than the bubo. The incidence of carbuncles varies in the epidemics from 10 to 15 per cent being a fair average.<sup>30</sup> Araujo<sup>31</sup> in a recent report found skin manifestations in only 7 per cent. Other skin manifestations are erythema pustules vesicles, bullae and hemorrhagic lesions. The latter are supposed to be so common and their appearance so ominous that from them originated the name of black death as the disease was called during the great European outbreaks in the Middle Ages. Such large fulminant hemorrhagic skin lesions have

<sup>28</sup>Gersh I and Black W O. Histology of Cutaneous Reaction to *Brucella Melitensis* Antigen. Arch Path 27 307-312, 1939.

<sup>29</sup>Lloyd, B J. Personal Experience With Bubonic Plague. J Trop Med 44 119-123, 1941.

<sup>30</sup>Müller H F and Pöck, B. Die Pest. 'Neuhausner' Specific Pathologie und Therapie Vienna, 1900. Alfred Hölder.

<sup>31</sup>Arajo E. Hanterschreibungen bei Pest. Statistisches, Klinisches, Pathogenetisches, Bruch-med 24 1-4 1921 Ekt 4 152.

not been noticed in the large plague epidemics of modern times. However petechial rashes occur which contain bacilli and therefore are a true metastatic infection (Albrecht and Ghon after Müller and Pösch<sup>291</sup>) Hemorrhagic streaks around the navel and in other sites have been recorded<sup>281</sup>

A rare occurrence are the papulopustular generalized dense varioliform exanthema.<sup>292</sup>

### Tularemia

Tularemia is named after the California county of Tulare where it was first observed among squirrels by McCoy<sup>293</sup> In man it is usually acquired by the handling especially skinning of wild rabbits, hares squirrels and other rodents, or by eating the insufficiently cooked meat from them. It has been shown to be carried by ticks<sup>294-296</sup> bedbugs<sup>297</sup> and other insects.<sup>298</sup> Laboratory infections have occurred in a considerable number although no contagion from man to man has become known except for one case of a physician at an autopsy (Weilbacher and Moss after Robert<sup>299</sup>)

The cause is a small pleomorphic gram-negative bacterium, *Pasteurella tularensis* which seems to be able to penetrate the unbroken skin as well as the mucosa. The incubation period is most often four days but it varies considerably. In traumatic infections the first symptoms at the site of the injury may develop after a few hours.<sup>300-302</sup> Fever may break out suddenly before any other symptoms even before the primary lesion appears.<sup>303</sup> This indicates the early dissemination of the infection. If the infection begins in the skin which is by far the most common way a primary lesion develops and the disease spreads along the lymphatics. The regional lymphatic vessels become indurated small nodules or bubonuli appear along them and bubos develop which may reach large size and may suppurate.

If the infection occurs in the conjunctival sac (1 per cent Hurst after Tassman<sup>304</sup> 3 per cent after Pullen and Stuart<sup>305</sup> 12 per cent Vrla after Robert<sup>299</sup>) or in the tonsils characteristic clinical pictures of long-lasting lid edema and suppurative lymphadenitis develop. The typhoid-resembling type, without apparent portal of infection is very rare. It has been seen in several laboratory infections. The severity of the infection varies from mild ambulatory cases with little fever and no internal complications to illnesses of many months duration sometimes with a fatal outcome. The mortality in the United States amounted

<sup>291</sup>Müller F. Reilly J. Chambredon, and Oshaka. Formes évanéssantes d'un pest. bactériologique. Bull. et Mem. Soc. Méd. Nat. Par. 48: 824-831 1925

<sup>292</sup>McCoy G. W. and Chapin, C. W. Tularemia. Bull. 43 Hyg. Lab. U. S. P. H. S. 1911

<sup>293</sup>Davis, G. E. Philip, C. B. and Parker R. R. Isolation From the Rocky Mountain Wood Tick of *Bacterium Tularensis*. Am. J. H. 18: 449-456, 1924

<sup>294</sup>Hyland, G. V. Breslow L. Crow, H. R. J. and Hershey W. J. Tick Borne Tularemia. J. A. M. A. 137 191-196, 1948

<sup>295</sup>Bogdanov V. Bedbugs as Carriers of Tularemia. Vestnik mlk 14 434 1923 Zh. 61 211

<sup>296</sup>Miller H. E. and Tassman, L. R. Tularemia. Arch. Derm. & Syph. 19: 874-880, 1929

<sup>297</sup>Robert, F. Tularemia Review of Literature. Dermatologica 99: 104-107 1920

<sup>298</sup>Pullen, R. L. and Stuart, B. M. Tularemia. 228 Comm. J. A. M. A. 129 496-500, 1924

<sup>299</sup>Robert, F. M. Tularemia and Pneumonia. Am. J. M. Sc. 261 233, 1944

<sup>300</sup>Davis, G. E. Die Bubonformen der Tularämie. Zentralbl. f. Bakt. 67 12(1-125), 1940.

<sup>301</sup>Tassman, J. R. Eye Manifestations of Internal Disorders. St. Louis, 1942. The C. V. Mosby Company

to 4.8 per cent among 7 077 cases reported from 1924 to 1936<sup>244</sup>. The autopsy findings often resembled those of tuberculosis.<sup>245,246</sup> There are miliary gray foci in the enlarged spleen and less often in the liver and in the lungs, which may show pneumonia or abscess. The microscopic picture of the lymph nodes and the subcutaneous nodules is that of an infectious granuloma<sup>247</sup> with epithelioid cells, lymphocytes and giant cells of the Langhans type creating a great similarity to tuberculosis.<sup>247</sup>

The microorganism can be isolated from the blood of the patient by inoculation into guinea pigs and by culture. This however is hardly possible after the first two weeks<sup>248</sup> and it has rarely been accomplished from an open lesion.<sup>24</sup> Agglutination in serum dilutions above 1:80 is considered diagnostic.<sup>24</sup> Skin allergy to tularemia<sup>241</sup> develops as early as four days after infection or even sooner.<sup>223</sup> The intracutaneous test with 0.02 or 0.05 c.c. of a bacterial suspension is read after forty-eight hours. The disease seems to leave the patients immune.

The treatment is symptomatic. The value of antiserum derived from goats<sup>223</sup> which has been found effective in reducing the severity and duration of the disease<sup>249</sup> needs confirmation. The beneficial effect of the sulfonamides is not generally confirmed.<sup>244</sup> Streptomycin is now considered to be the drug of choice.

**Dermadromes.**—The primary lesion may occur almost anywhere on the skin. It may be single or there may be multiple lesions. The primary lesion appears after a period of about one week when general dissemination has already manifested itself by fever and malaise. Even the regional lymph nodes may become enlarged and tender before the appearance of the primary lesion. The initial lesion is a papule the center of which soon becomes depressed and necrotic, forming a punched-out ulcer with raised edges. This ulcer is painful and defies therapy but after several weeks it heals spontaneously.<sup>246</sup> The early lesions of tularemia may imitate syphilis, anthrax, felon or other conditions. Due to the lymphatic chain of nodules or abscesses the picture may closely resemble sporotrichosis or primary inoculation tuberculosis.<sup>242,243</sup>

In the primary stage the diagnosis often can be secured only by the intracutaneous test.

The bubonuli and lymph nodes may become tender, adhere to the skin and ulcerate. In one case reported by Blackford and Smith (quoted after Hitch

<sup>244</sup>Christening H. S. Tularemia. Bull. Office Internat. d'Hyg. Pub. 29: 2532 1937.

<sup>245</sup>Quincy L. P. and Warner O. B. Fatal Tularemia. 15 *A. Topics, Ann. Int. Med.* 7: 837-852 1934.

<sup>246</sup>Lawson, J. N. Tularemia. Arch. Dermat. & Syph. 44: 147-160 1941.

<sup>247</sup>Gl. W. H. and Jacob F. M. Tularemia. Arch. Dermat. & Syph. 21: 900, 1921.

<sup>248</sup>Hitch, T. M. and Smith, D. O. Cutaneous Manifestations of Tularemia. Arch. Dermat. & Syph. 29: 859-876 1934.

<sup>249</sup>Nicholson E. W. Tularemia. Cutaneous Manifestations. Arch. Dermat. & Syph. 16: 170-1 1927.

<sup>250</sup>Pasterback J. H. Tularemia. Initial Buboes. F. Boston Tick Bites. J. A. M. A. 212: 1816-1817 1939.

<sup>251</sup>Payday L. Tularemia. Farlier Diagnosis by Intradermal Reaction. J. Infect. Dis. 51: 254, 1932.

<sup>252</sup>Parson H. W. Interesting Cases of Tularemia. Tri-Stat. M. J. 12: 2705-2714 1911.

<sup>253</sup>Payday L. Tularemia Treated by New Specific Antivenom. Am. J. M. Sc. 187: 225-245 1924.

<sup>254</sup>Wentzler, E. H. Tularemia. 10 Cases. J. Oklahoma M. A. 28: 103-104 1913.

<sup>255</sup>Chalmers H. Tularemia Resembling Sporotrichosis. Arch. Dermat. & Syph. 19: 913-921 1929.

and Smith<sup>300</sup>) fungating growths developed out of such bubonuli. The histological structure of the subcutaneous nodules is definitely tuberculoid.

Generalized eruptions are a feature of the disease but they occur only in a fraction of the cases (8 per cent after Pullen and Stuart<sup>301</sup>) and are not characterized by any specific morphology. Hitch and Smith<sup>302</sup> surveyed forty-eight cases of secondary eruption in tularemia. They demonstrated that eruptions occur in all types of the disease most often in the second week and that the average duration is three weeks. However great deviation of the average figures is



Fig 3 —Tularemia. Erythema nodosum and ulcers resembling eruption on fifteenth day of the disease. (From Hitch, J M and Smith Dudley C. Arch Dermat., 1935.)



Fig 34 —Tularemia. Papular rash. Courtesy Dr. W. Lee M. Ranspau, from Sutton and Sutton, Diseases of the Skin, The C. V. Mosby Company.)

frequently observed. Pleomorphism is a characteristic feature. The most commonly encountered morphologic type was the *papular* eruption which was seen in approximately one half of the eruptive cases. Less common are macules, pustules, vesicles, wheals, nodules, ulcerations and transitional forms. The rashes often gave the impression of erythema multiforme, sometimes with herpes lesions. The eruptions were generalized or they involved only a part of the body, mostly the upper trunk and the arms especially on the side of the primary lesion. In ophthalmic cases a facial eruption appeared on the side of the infected eye. The eruptive cases did not differ from the noneruptive ones with regard to incubation period or agglutination titer. The histological examination did not reveal changes other than one might expect, that is edema and perivascular lymphocytic and fibroblastic infiltration. The common appearance of the rashes after the period of bacteremia and fever supports the conception of the toxic rather than infectious nature of the secondary rashes in tularemia.

The prognosis of the secondary rashes is good; the treatment is symptomatic.



Fig. 37.—Primary lesions of tularemia and lymphangitis at works after onset. (courtesy Dr. Walter M. Altmeyer from Rosen and Burton, *Diseases of the Skin*, The C. V. Mosby Company.)

### Erythema Arthriticum Epidemicum Ratbite Fever or Haverhill Fever

Erythema arthriticum epidemicum, ratbite fever, Haverhill fever\*—none of these three names is correct. The disease is not always epidemic, does not always follow a rat bite, and Haverhill Mass. is neither the only nor the first place where it was observed. Erythema arthriticum would be a good name but the term Haverhill fever has become established.

The disease is an acute infection which usually follows a rat bite. It should not be confused with *sodoku* which is also transmitted by rat bites. While the ratbite cases occur sporadically,<sup>71</sup> a milk-borne epidemic with eighty-six cases

\*For bibliography of the ratbite fevers, see Press, T. M. and Kemeraker, T. G.: *Bull. Johns Hopkins Hosp.* 79: 201-205, 1917.

<sup>71</sup>Farrell, E. Leeds, C. H. and Vogel, T. H.: *Haverhill Fever. Case With Review of Literature*. Arch. Intern. Med. 64: 14, 1939.

was observed in Haverhill Mass. in 1926<sup>21</sup> and another milk borne—not quite verified—outbreak of 600 cases at Chester Pa. (Armstrong and H. Wood after Place and Sutton<sup>21b</sup>). The epidemic and sporadic forms are caused by the nonmotile pleomorphic gram negative and nonacid-fast *Streptobacillus moniliformis* (Haverhillia multiformis)<sup>21c</sup> which during the fever can be cultured from the blood of the patient. Mice die from the disease forty-eight hours after intra peritoneal injection of blood.

About three days after the infecting bite of rats, who often harbor the microorganism in their pharynx, the disease starts quite suddenly with malaise, headache, chill and high fever. A rash and acute polyarthritis develop early and heal after several days. There is a leukocytosis of over 12 000. The spleen is not enlarged. There were no fatalities in the Haverhill epidemic. A rash was observed in 94 per cent of the Haverhill cases which appeared during the first week, most often between the second and fifth days. It involved predominantly the lateral and distal extensor surfaces of the extremities rarely the trunk and face. There is sometimes accentuation around the joints.<sup>22</sup> The exanthem has been described as a maculopapular rubelliform or morbilliform vividly red eruption with the efflorescences being about 3 to 5 mm. in size.<sup>23</sup> In some cases the exanthem had the characteristics of erythema exudativum multiforme (Levaditi, Nicolau and Poincloux after Farrel and associates<sup>24</sup>). The rash usually fades after one week, with little desquamation or pigmentation. The exanthem may reappear with new paroxysms of the fever. Then it is likely to be more confluent.<sup>25</sup> A hemorrhagic tendency can be demonstrated by a positive tourniquet test and by pin point hemorrhages in the center of the lesions.

In the cases studied by Albritten, Sheely and Jeffers,<sup>26</sup> tender purpuric nodules with yellow nonsuppurative, depressed centers, resembling those seen in subacute bacterial endocarditis, appeared around the finger tips. They probably are metastatic embolic foci. Lymphadenopathy in relation to the site of the bite is rare.<sup>27</sup>

The diagnosis rests on the history of a rat bite and the laboratory findings. Agglutination tests are known. A cutaneous reaction to suspensions of killed streptobacilli was present in 83 per cent of the Haverhill patients tested late in convalescence. It seems important to compare the symptomatology of Haverhill fever and that of sodoku, the other ratbite disease, which may occasionally cause a syndrome quite indistinguishable from Haverhill fever.<sup>28</sup> Usually sodoku (see under sodoku) presents a chancreform induration at the bitten area which is followed by lymphangitis. Arthritis is rare. The causative organisms of both diseases are penicillin sensitive (Wheeler after Fleming<sup>29</sup>).

<sup>21</sup> Place, E. H., Armstrong, L. E. and Wheeler, O.: Erythema Arthritic in Epidemicum. Preliminary Report, Boston M. & S. J. 194: 268-287 1926.

<sup>21b</sup> Place, F. H. and Armstrong, L. E.: Haverhill Fever Arch. I. Vol. 84: 654 1924.

<sup>21c</sup> Packer, F. J. and Hadwen, N. P.: Haverhill Fever. Am. J. Path. 2: 257 1926.

<sup>22</sup> Albritten, F. F., Sheely, R. F. and Jeffers, W. A.: Haverhillia Multiformis Septicemia Relationship of Erythema Exudativum to Foci. J. A. M. A. 814: 3260-3263 1920.

<sup>23</sup> DeWitt, T. J. and Nunnemacher, J. C.: Rat-bite Fever. Review of American Cases. Bull. J. Nat. Hygiene Hosp. 79: 201-242.

## Glanders (Malleus)

Glanders (malleus) occurs predominantly and in large epizootics among horses from which most of the rare human cases originate. A number of laboratory infections have become known.<sup>221</sup> The disease which has an incubation period of from three to five days is caused by the pleomorphic nonmotile bacillus *Malleomyces mallei*. The germ enters the human body through the skin or through the mucosa possibly without a wound. From a primary lesion the disease spreads and frequently becomes generalized taking an acute or irregularly relapsing chronic course of unfavorable prognosis. Specific lesions may occur in any organ but there is a definite cutaneous and mucosal affinity. The predominantly lymphangitic form is sometimes called farcy while the term glanders is often used for those cases in which the mucosal especially the rhinitic involvement dominates the picture. Not very long ago the two forms were believed to be different entities. The specific malleus lesions are granulomas which resemble tuberculosis in many ways.

The diagnosis rests on a history of contact with horses or mules the unusual clinical picture the microscopic and cultural evidence of *Malleomyces mallei* the intraperitoneal inoculation into the male guinea pig followed by the specific inflammation of the testes and various serological and allergic tests among which the complement fixation the ophthalmic and the intracutaneous tests have been used in man.

**Dermadromes**—The primary lesion which has been most often observed on the hands and arms the face and the conjunctiva is a furuncle-like infiltration which soon breaks down in the center and forms an ulcer with jagged raised livid and infiltrated edges and a necrotic floor with edematous and erythematous surroundings.<sup>222</sup> The lesion may reach dollar size but it finally heals spontaneously. In some cases it fails to develop so that lymphangitis appears as the first cutaneous symptom. Lymphangitis without noticeable lymphadenitis is a peculiar feature of malleus in human beings.<sup>223</sup> The wire or pencil like lymphatics are palpable along the extremity and small bubonuli (buds) develop alongside the vessels. This type of lymphangitis resembles sporotrichosis or tuberculosis. Sinuses, sieve like perforations ulcers and scars may develop. In rare instances the disease becomes chronic in this stage. The primary lesion of the oral or nasal mucosa is an ulcer similar to that of the skin.

General systemic infection follows the majority of the primary lesions. The period after which systemic symptoms appear may be a few days to many weeks or months. The skin manifestations of the systemic infection have a predilection for the nose and face. These secondary malleids appear in crops and show great differences in severity grouping and number. The exanthem usually starts as a roseola. The maculae which in rare instances are purpuric, become papular papulopustular and later ulcerative. They are occasionally bullous or composed

<sup>221</sup>Roosli J W. Acute Glanders Case Nederl. Tijdschr. Geneesk. 23: 3273-3281 1929 Ed. 23: 279

<sup>222</sup>Bierbaum E and Gottroff H. Notiz (Malleus) Handb. d. H. Ch. 3: 355-396 1929

of concentric rings<sup>224</sup> resembling erythema multiforme. These ulcers may by infiltration of the surroundings and by coalescence grow to larger plaques which may also develop from cutaneous or subcutaneous nodules. Breaking down of nodules or plaques may cause deep destruction of the muscles and tendons and even affect the joints.<sup>225</sup> Destructive and suppurative lesions in and around the nose may cause a peculiar swelling and erythema of the nose which has been termed by de Balogh<sup>226</sup> who reported eight cases, potato nose. This author describes nonsuppurative livid nodules in the face as typical secondary lesions.

The histology of the fully developed lesions shows granulation tissue composed predominantly of leukocytes and to a lesser degree of epithelioid plasma and mast cells. There is a pronounced necrotic tendency. Karyorrhexis is a feature and bacilli may occur in large numbers.

Sporotrichosis, tuberculosis and pyogenic lymphangitis must be considered in the lymphangitic period and syphilis and mycosis fungoides in the later systemic stages. The common concentration around the nose and the necrotic tendency of the granuloma support the clinical diagnosis of malleus. However considering the rarity of human glanders and the many varieties of its course all laboratory methods must be employed.

Generalized glanders in man is, almost without exception a fatal disease. Chronic localized malleus heals spontaneously in about 50 per cent of the cases (Bollinger after Bierbaum and Gottron<sup>227</sup>). No specific treatment is known.

### Cholera Asiatica

Cholera asiatica is an acute often epidemic infection caused by the *Vibrio comma* (Koch). In its severest fulminating form the disease may run a fatal course in from three to four hours but less severe forms are well known. The outstanding symptoms are excessive watery diarrhea, dehydration and circulatory collapse.

Dermadromes.—The skin is described as pale or cyanotic even livid covered with sweat wrinkled and withered. Urea frost has often been seen covering such dehydrated patients. In fact this sign was described in cholera long before its association with uremia was noted (Schottin after Chargin and Keil<sup>228</sup>). In cholera there is a pronounced tendency to necrosis and decubiti.<sup>229</sup> Exanthems are infrequent.

The older literature contains a number of references. Liebermeister<sup>230</sup> in a monograph written after the great epidemic of 17 000 cases in Hamburg Germany in 1892 denied the existence of a specific exanthem at the height of the disease. In the early stages of recovery cyanotic spots may remain as remnants

<sup>224</sup>Levitzky A. Leber-elsen Fall on skin cat Rots, Bruns Beitr. z. klin. Chir. 128: 422-443 1923

<sup>225</sup>Balogh E. de his Lesions in Human Glanders, Verh. 9 Internat. Kongr. Dermat. 2: 427-431 1926

<sup>226</sup>Chargin L. and Keil H. Skin Disease in Nonsurgical Resal Disease Arch. Dermat. & Syph. 25: 314-323 1922

<sup>227</sup>Keil H. and Doerr R. Cholera Asiatica. Handbuch der inneren Medizin, Berlin, 1923, Julius Springer

<sup>228</sup>Liebermeister O. Cholera Asiatica and Cholera nostras, Netzhager's Special Pathologie und Therapie, Vienna, 1896 Alfred Holder



of the collapse of circulation during the attack. Roseola and other erythemas especially of the erythema multiforme type papules vesicles urticaria and petechiae have occasionally been seen but the specific character of these rashes has not been demonstrated. Some may have been drug eruptions.<sup>27</sup>

### Whooping Cough

During the characteristic attacks the glottis is temporarily closed and at the termination of the spell it is opened for a long-drawn crowing inspiration.<sup>28</sup> The disease is caused by a small bacillus with accentuated poles discovered by Bordet and Gengou.

**Dermadromes**—The repeated severe coughing spells frequently produce some puffiness around the eyes especially of the upper lids together with slight chemosis. This is known as the *whooping cough face*. *Petechiae* which are quite rare in the skin occur more frequently in the mucosae especially in the conjunctivae of young children. Both *bulbar conjunctivae may be deep red* a terrifying but harmless sign.

The vesicles of a *varicella exanthem* coinciding with whooping cough may become *hemorrhagic* due to the coughing bouts. This is especially true of the vesicles in the area drained by the upper vena cava.<sup>29</sup> The violent fluctuations of vascular pressure during the cough and possibly the infectious and toxic damage to the capillaries may prepare the rhexis of the capillaries.

**Cutaneous emphysema** is a rare but dangerous complication of whooping cough. It is caused by the rupture of alveolar vesicles due to the high intra-pulmonary pressure. From the ruptured lung the air is pressed under the pleura which on autopsy has been seen to be separated from the lung. The air follows the mediastinum and finally reaches the skin of the neck or chest.

A well known complication of whooping cough is the *shallow ulceration of the frenulum linguae*. It results from injury and irritation of the frenulum caused during the coughing by the incisor teeth or in the absence of teeth by the hard lower jaw.

### Diphtheria

Exanthems indicative of generalized diphtheric infection are rare. Some rashes have been interpreted as initial exanthems since they occurred during the first day.<sup>30</sup>

Purpuric, morbilliform, scarlatiniform, papular and vesicular eruptions resembling erythema nodosum and multiforme, and even typhoidlike rose spots have been described. Allowance must be made for drug eruptions, true scarlet fever<sup>31</sup> and serum exanthems.

*Herpes* seems to be rarer than in many other infectious diseases. The herpes vesicles may contain bacilli (Rall after Biberstein<sup>32</sup>)

<sup>27</sup>Koepfhauser W. Whooping Cough Pfander and Schlossmann: The Diseases of Children, vol. III Philadelphia, 1933 J. B. Lippincott Company pp. 336-351.

<sup>28</sup>Biberstein, H. Die Difterie der Haut, Handb. d. H. Gk. 9, S. 145-162 1929.

<sup>29</sup>Russ, P. Esantoni scarlatinalforal scleroterapia nel corso della difteri. Scrittura dedicata Carlo Coma Riv. di clin. pediat. 27 426-433, 1929.

### Panniculitis (Weber-Christian Disease)

Twenty-eight cases of a syndrome of relapsing febrile, nodular nonsuppurative panniculitis (Weber-Christian disease) have been reported since 1892<sup>300</sup>. There are crops of cutaneous and subcutaneous painless or tender nodules, mostly on the thighs and arms but also on the trunk, and accompanied by fever. The lesions are the expression of an inflammatory process which results in atrophy of the subcutaneous fat producing in the skin lasting depressions of a varying depth and width. Fever is a constant symptom. Two cases were fatal. The etiology and even the clinical entity itself are still controversial. Focal infection, tuberculosis, eruptions from iodine or bromides, and other causes have been considered<sup>301</sup>.

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<sup>300</sup>Pfeifer, V. Ueber einen Fall von herdförmiger Atrophie des subcutanen Fettgewebes, *Deutsches Arch. f. klin. Med.* 54: 438-440, 1892.

<sup>301</sup>Larkin, V. P., De Sanctis, A. G. and Margulies, A. B. Panniculitis—Review of Literature. *Am. J. Dis. Child.* 87: 120-123, 1944.

## CHAPTER IV

### SYSTEMIC INFECTIONS

#### Influenza

Influenza is almost certainly caused by at least three different types of virus<sup>224</sup> now called A B and V but is usually complicated by the secondary invasion of various bacilli especially the Pfeiffer bacillus the pneumococcus and the pyogenic cocci. Sporadic cases occur although epidemics and pandemics are characteristic of the disease. Influenza is very contagious. The incubation period is short about two days. The onset is quite sudden sometimes with marked catarrhal symptoms or sore throat. The fever is irregular and chills and remissions are common. The respiratory tract in its full length is inflamed bronchitis and pneumonia are serious complications which in 1918 caused most of the deaths.<sup>225</sup> Prostration is often marked and not explained by the temperature alone. Gastrointestinal symptoms and sometimes severe and irreversible lesions of the nervous system may in a small minority of cases dominate the picture. Many other complications are known. Mild leukopenia is common before secondary infection supervenes.

The post mortem findings concern chiefly the respiratory tract.

The mortality varies from 15 to 60 per cent depending on the character of the epidemic<sup>226</sup> although exact figures are not available. In 1918-1919 at the time of the last influenza pandemic there were 550 000 deaths in the United States in excess of the normal expectancy. No specific treatment has been discovered as yet.

**Dermadromes**—The skin manifestations are neither impressive nor of diagnostic importance. They rarely influence the course or cause suffering to the patient.<sup>227</sup> The incidence of skin and oral symptoms given by various authors varies from 1 to 20 per cent. However such percentages are of little value in a disease which in many cases is difficult to differentiate from other common respiratory infections.

During the febrile period *herpes simplex* is common and sometimes develops even after the temperature has returned to normal. The appearance of herpes does not seem to depend on the respiratory involvement.<sup>227</sup>

*Exanthems* of great variability have often been noticed usually in the early stages of the infection. These skin eruptions are most often macular<sup>228</sup> or mor-

<sup>224</sup>Jefferson F. L. J. *Present Status of Influenza* J. A. M. A. 120: 245-247 1912.

<sup>225</sup>Top F. H. *Communicable Diseases St. Louis 1911 The C. V. Mosby Co.* p. 118.

<sup>226</sup>Schütz H. *Dermatologie und Grippe* Med. Welt 23: 1808-1810 1919.

<sup>227</sup>Schaumacher O. and Moncorps C. *Haut- und Schleimhauterkrankungen bei Grippe* Zbl. B. 190: 291 1915.

<sup>228</sup>Freund *Grippexantheme* Zbl. B. 23: 625.

bulliform<sup>323</sup> less frequently scarlatiniform.<sup>340</sup> Besides these main types, urticarial, vivid red papular<sup>341</sup> purpuric, and spotted typhuslike rashes have been recorded. There are combinations of macular and hemorrhagic lesions.<sup>342</sup> The serious prognostic significance of purpuric rashes is often emphasized. Erythema nodosum and erythema exudativum multiforme<sup>343</sup> have been observed in a considerable number of cases.

Most of the influenza rashes are very transitory.<sup>324,344</sup> The difficulty in differentiation from measles, scarlet fever, and other exanthematic diseases is often great. A carefully taken history of contacts and previous diseases, consideration of the incubation period, and negative results of the diagnostic procedures used in other infections will usually help to overcome the difficulties. In sporadic cases the diagnosis may be made only after further observation of the course. Jordan<sup>345</sup> emphasizes the lack of adenopathy as a criterion against rubella.



Fig. 22.—Virus tongue in influenza. The tongue is large, flabby, and shows dental impressions. (Courtesy Dr. Max Fox.)

In the oral mucosa circumscribed erythema of the soft palate and the posterior tongue and a buccal exanthem not unlike Koplik's spots in measles are common.<sup>347</sup> A flabby slightly edematous tongue showing marginal impressions of the teeth (virus tongue) is often considered characteristic of influenza and other virus diseases. The pharyngeal involvement may occasionally become severe. Follicular tonsillitis, pseudomembranes of the pharynx, and small ulcerations of the mucosa may even lead to glottic edema.

<sup>323</sup>Optiz, H. Grippe- und Keuchhusten. *Kindervärzt.* Frankfurt 154-156, 1923.

<sup>340</sup>Koch, H. Exanthem bei grippeartigen Erkrankungen. *Wien med. Wchnsch.* 79: 333, 1923.

<sup>341</sup>Deasy, G. Rube manifestazioni papulari cutanee della influenza. *Riforma med.* 83: 812-819, 1927.

<sup>342</sup>Leichtentritt, B. and Schober, W. Grippeexantheme. *Klin. Wchnsch.* 3: 1029-1032, 1924.

<sup>343</sup>Oppenheim. Grippeexantheme. *Zbl.* 23: 742.

<sup>344</sup>Jordan, A. Ueber Grippeauschläge. *Dermat. Wchnsch.* 61: 1011-1014, 1920.

Following the acute period erysipelas of the face has often been observed especially in the older epidemics. Other common cutaneous sequelae are furunculosis and herpes zoster. Symmetric gangrene of the extremities is an exceedingly rare event.<sup>146</sup>

Alopecia diffusa was a common dermatome during the epidemic of 1918. The shedding of the hair after influenza was often troublesome although the hair usually grew back. Beau's lines of the nails were often observed. The dermatomes of influenzal encephalitis will be discussed in Chapter XXXIX.

### Measles

It is generally agreed that measles is caused by a filtrable virus which lately has been cultured in the chick embryo<sup>147</sup> (Kunert and Wenkebach after Rietschel<sup>148</sup> and successfully inoculated into the child after several passages.



Fig. 30.—Measles, fifth day. Exanthem and conjunctivitis. (Courtesy Dr M. Fox.)

The disease is highly contagious among persons who have not had much exposure to the virus and therefore, is predominantly a child's disease. Measles

<sup>146</sup>Mott, A. Gangrène aiguë symétrique des extrémités post-grippale. Gaz. méd. de France 48 649-650 1929.

<sup>147</sup>Rietschel, H. Measles, Review of Literature. Monatsschr. f. Kinderh. 88 312-356 1911.

<sup>148</sup>Bake H. and Schaffer M. F. Studies of Measles. Use of Chorio-Allantoic of Developing Chicken Embryo. J. Immunol. 28 177 1940.

is most contagious about twenty four hours before the eruption. With the appearance of the exanthem the infectivity decreases rapidly and is nil at the time of desquamation. The infectious agent is present in the respiratory tract and in the blood and it has also been demonstrated in artificial blisters of the skin. Lifelong specific immunity after measles is the rule, true reinfection being extremely rare.

The first catarrhal symptoms appear not too suddenly after an incubation period of about ten days. Headache, anorexia, conjunctivitis and coryza sometimes with nosebleed, cough, vomiting and sudden fever are the common prodromal symptoms. On the first day the lower lids may be slightly puffy and a fairly definite erythematous transverse line appears across the conjunctival surface of the lower eyelid about a third of the distance from the lid margin to the fornix (Stimson after Sobel in Mackee and Cipollaro<sup>40</sup>).

On the second day of the prodromal stage a few (from six to twenty) pin point sized white spots, often surrounded by a bright red, at first narrow but soon widening areola, appear on the buccal and later often on the labial mucosa. This prodromal mucosal eruption which is commonly known as Koplik's spots is of great diagnostic importance since it hardly occurs in other diseases and it can be seen in about 90 per cent of the measles cases, preceding the outbreak of the exanthem. The Koplik spots vanish when the rash appears and are soon followed by an exanthem of dark red spots of pin head to lentil size which may coalesce into large spots scattered over the soft palate and later over greater areas. Koplik's spots may be absent in the measles of small children.<sup>41</sup>

The temperature usually drops on the second day only to rise again during the next two days. Between the third and fifth days (two weeks after the infection) the rash appears. The disease reaches its height around the fifth day and from that time on the symptoms are eased. On the seventh or eighth day after the full development of the rash the temperature gradually becomes normal, the rash fades, and the catarrhal symptoms are no longer annoying. Recovery follows gradually. Cervical adenopathy is common but is mild and rarely leads to abscesses.

The clinical picture is dominated by the rash and the intense catarrhal involvement of the mucous membranes, particularly of the respiratory tract and of the eyes. There is leukopenia at the height of the rash, mainly caused by a drop in the lymphocytes.

The list of possible complications is long but fortunately the overwhelming majority of the patients recover uneventfully.

**Dermadromes.**—Pale scarlatiniform or macular premonitory rashes are rare and very fleeting<sup>42,43,44</sup> and may disappear before the outbreak of the measles rash.

<sup>40</sup>G. Mackee, E. Deskritische Dreitagefieberexanthem beim der kleinen Kinder (Exanthema subitum) Ergebn. d. intern. Med. u. Kinderh. 23: 68-80, 1929.

<sup>41</sup>Stimson, A. Minor observations, prodromal exanthem, Med. Klin. 22: 496, 1927.

<sup>42</sup>W. Wietand, Ueber Fieberhaften scarlatiniformen Rash bei Measeln, Monatsschr. f. Kinderh. 42: 432-434, 1929.

<sup>43</sup>M. Hirsch, Ueber J. Vaccinatum bei Measeln, Jahrb. f. Kinderh. 86: 2: 222, 1922.

The *exanthem*<sup>291</sup> (Von Pirquet in Von Groer<sup>292</sup>) starts with pale pink spots from 1 to 5 mm in diameter. Intense itching may accompany the eruption. The spots are seen clearly first on the scalp behind the ears and between the shoulder blades, less distinctly around the mouth and nose and in front of the ears. The cheeks offer a certain resistance but are soon invaded also. On the second day a dense exanthem appears on the back and although less pronounced on the chest, abdomen and mesial aspects of the arms. On the third and fourth days the development is completed with the invasion of the legs. The emphasis



Fig. 40.—Measles. (Courtesy Dr. Max Fox.)

is on the head, trunk, shoulders and anterior surfaces of the arms and thighs. On the fifth day the appearance of new lesions usually stops. With the return to normal temperature the spots fade in the order of their appearance, leaving a pigmentation which is sometimes quite pronounced on the forehead. There is a superficial branny desquamation which usually starts on the face from two to five days after the appearance of the exanthem.<sup>293</sup>

The first lesions are follicular spots or slightly palpable papules surrounded by an anemic halo. They grow quickly in size and number and become confluent, but the original follicular papular character can still be recognized within the larger bright red spots of the developed exanthem. There is a great variability

<sup>291</sup> Von Örder, F. Measles. Pfäunders and Schloerwald. Diseases of Children, vol. III Philadelphia 1935. J. B. Lippincott Company pp. 170-212.

<sup>292</sup> Kolby, F. Akute Exantheme. Handbuch der inneren Medizin, ed. I Berlin 1924. Jahnke Springer.

<sup>293</sup> Reuband, A. Über Hautschuppung nach Masern. Jahrb. f. Kinderh. 118, 203-224 1927.

in the exanthema with regard to size of lesions, density and tendency to remain discrete or become more confluent. At its height the eruption is blotchy and dusky red. Miliary vesicles are quite common on the follicular papules. Increased seborrhoeic activity makes the skin feel greasy. The tourniquet test is usually positive.

While the exanthema may vary great similarities of the rash in siblings as well as in individual epidemics have been observed indicating the power of constitutional and microbic factors.

The histopathology of the measles<sup>330</sup> exanthem is characterized by vacuolization in the epidermis and a perivascular predominantly lymphocytic infiltrate in the papillary body. There are small necrotic areas which correspond to macroscopic pustules. The absence of a horny layer in the oral mucosa produces the early erosions of the Koplik spots. It is not for very long that anything has been known about the peculiar formation of giant cells with 50 to 100 nuclei which occur in the lymphatic tissue of the tonsils, the respiratory tract and the esophagus, and which have been seen in appendices removed during measles (Warthin and Finkelday after Ravina and Levy Lang<sup>331</sup>; Manigi and Minami after Rietchel<sup>340</sup>).

Among the anomalies of the exanthem must be named first its absence, morbilli sine exanthemate. Usually the Koplik spots too are absent in such cases,<sup>341</sup> of which a great number have been well corroborated by the presence of all other symptoms, by the incubation period and by contact cases.<sup>342-347</sup>

While miliaria is common, bullous measles are rare. Confluent large bullae may though rarely cover and denude large areas so that the clinical picture of pemphigus results.<sup>348</sup> Hemorrhagic measles is rare; this variety has been seen in combination with bullous measles.<sup>349</sup> Swelling of the upper lip of two to three days' duration is in some epidemics so common that one author has spoken of a measles lip (Orems after Robert<sup>350</sup>).

Measles, especially the hemorrhagic form, is sometimes followed by gangrene of localized areas of the skin.<sup>351-353</sup> Related to these cases are the multiple ulcerations which are known as *ecthyma gangrenosum*<sup>354</sup> which are occasionally seen after other infections too, usually affecting infants. Ecthyma gangrenosum starts on the buttocks with hemorrhagic necrotic nodules or larger foci of cellulitis and leads to deep punched-out ulcers. The mortality is high. The condition is probably caused by secondary infection, especially with pyogenic cocci and *Pseudomonas aeruginosa* (*Bacillus pyocyaneus*).

<sup>330</sup>Ravina, A. and Levy Lang, P. Histologic Diagnosis of Measles. Specificity of Giant Cells. Appendicitis Caused by 3 cases. Presse med. 48: 831-833, 1937.

<sup>331</sup>Krawasani, E. 3 cases sine Exanthem bei drei Geschwistern Monatschr. f. Kinderh. 27: 810-811, 1914.

<sup>332</sup>Koeppe, H. 3 acuta sine Exanthem. Arch. f. Kinderh. 84: 190-193, 1929.

<sup>333</sup>Wiegner, G. Pemphigoider bullöser 3 acuta und Pemphigus bei Masern. Monatschr. f. Kinderh. 27: 812-815, 1924.

<sup>334</sup>Liesner, J. J. Hemorrhagic 3 cases. Brit. M. J. 2: 755, 1913.

<sup>335</sup>Robert, P. Infectious Skin Diseases Other Than Tuberculosis and Leprosy. Review of Literature. Dermatologica 27: 3-333, 1913.

<sup>336</sup>Thorp, E. A Case of Gangrene Following Measles. Lancet 261: 754, 1921.

<sup>337</sup>Winstead, J. A. In grege f. the Foot Following Measles. J. Pediat. 6: 340-344, 1913.

<sup>338</sup>Takahashi, K. b. w. gangrenosum im Verlauf von Masern. Arch. f. Dermat. u. Syph. 129: 729-730, 1914.



Measles may affect *pre-existing skin diseases* in various ways. Infantile eczema<sup>344</sup> and prurigo<sup>345</sup> are often aggravated during measles<sup>346</sup> either by internal causes or by scratching during the itching eruption and desquamation periods. Psoriasis seems to improve but returns during convalescence<sup>347</sup>. Measles like other acute infectious diseases often weakens the cutaneous tuberculin reaction. The predisposing influence to skin tuberculosis is recognized.<sup>348</sup> Disseminated exanthematic, apparently hematogenous cases of lupus vulgaris and tuberculous cutis verrucosa are not very rare after measles in countries where skin tuberculosis is more prevalent than in the United States.

### German Measles (Rubella)

The term German measles resulted from the long-combined efforts of German clinicians of the nineteenth century to separate a mild measles-like contagious disease from typical measles. When the International Medical Congress in London in 1881 tried to clarify the situation it was natural to speak of English measles and of German measles. Since then the entity has become widely recognized but there are still some dissenting unitarians. To prevent confusion it should be emphasized that the latin term rubeola is used for this disease in the German literature while in the English American terminology rubeola designates true measles (Dorland). The term rubella seems to be used only in the English-speaking countries.

The cause of the disease is unknown. Children of 3 to 10 years of age are usually affected but no age group is immune. Lasting immunity after the disease is the rule.

The disease is best characterized by the often used expression mild measles. The prodromal symptoms of malaise, fever, coryza and sore throat, which are not always present, are much less pronounced than in measles. Children with German measles frequently come to the office of the dermatologist or are sent home from school because of the rash while a child with true measles is usually too sick to be ambulatory.

The incubation period of rubella is from two to three weeks. The fever is moderate and there is no photophobia or conjunctivitis. Excessive perspiration during the first to second prodromal days is a peculiar symptom (Stolte after Rietschel<sup>349</sup>). The palate and uvula are reddened and a few red follicles often appear along the midline (Forchheimer's sign) but there are no Koplik spots and the catarrhal symptoms, if any, are mild.

General lymphadenopathy is such an outstanding feature of the disease that Glanzmann advanced the theory that rubella is a disease of the lymphatic system not primarily an exanthem and therefore *toto caelo*<sup>350</sup> different from measles.

<sup>344</sup>Berk, C. H. *Journal of the American Medical Association* 1935 101: 1187-1190 1935.  
<sup>345</sup>Vedert, H. *Archiv für Dermatologie und Syphilis* 1935 101: 1187-1190 1935.

<sup>346</sup>Costantini, O. *Sul comportamento dell'eczema del lattante durante il morbilli*, Clin. pediat. 1930 216-225 1930.

<sup>347</sup>Yolk, R. *Tuberkulose der Haut*, Handb. d. H. 1931 10: 1 1931.

<sup>348</sup>Rietschel, H. *Rubella*, Monatsschr. f. Kinderh. 98 242-245 1941.

and scarlet fever. Almost all the peripheral lymphatic nodes are swollen and tender and the mastoid, occipital and posterior cervical glands particularly of the left side are so enlarged that the swelling often is not only palpable but visible. The lymphadenopathy starts before the exanthem and may outlast it by several weeks. This generalized lymphadenitis may be the only sign of rubella. In such exanthemless cases the diagnosis must depend on the accompanying circumstances, for example, contact cases with exanthem.<sup>379</sup>



Fig. 41.—German measles. Quite copious rash. (Courtesy Dr. Max Fox.)

The blood shows an initial leukopenia and a later eosinophilia (8 per cent). In the course of the disease the leukocytes rise and the increase of the plasma cells becomes marked, reaching 12 per cent.<sup>379,478</sup>

The *prognosis* is very favorable. The *treatment* is symptomatic.

**Dermadromes.**—The exanthem which appears on the second or third day follows in many ways the pattern of measles. It is usually seen first behind the ears and on the nose but within one day it involves the whole body, occasionally large areas remain free. The fresh spots are rounder, more clearly defined and more regular than those of true measles. The most common size is that of a split pea, although the rash may consist of smaller or larger spots. The color is

<sup>379</sup>Kletzschel, H.: Acute Infectious Exanthema, *The Diseases of Children*, H. Praesler-Schlossmann-Prierman, vol. 111 Philadelphia, 1935, J. B. Lippincott Company, pp. 212-232.

<sup>478</sup>Kletzschel, H.: Masern und Röteln, *Monatsschr. f. Kinderh.* 71: 84-90, 1937.

<sup>479</sup>Wijayaratne, D.: Rubella Without Rash, *Brit. J. Child Dis.* 29: 20-23, 1932.

<sup>480</sup>Moravetz, H.: Röteln R. roths, *Handb. d. H.* 14: 1 437-439, 1930.

<sup>481</sup>Frederbach, Röteln, *Therap. u. Gegenw.* 53: 76-77, 1932.

red a shade less bright than in true measles and fades quickly. Often a confluent erythema develops on the face. The skin between the spots may especially on the back be diffusely red with the progress of the disease. Some epidemics have a pronounced hemorrhagic component.<sup>201</sup> The rash appears in successive crops, each of which lasts about twenty-four hours. The whole exanthem lasts about three days. It fades in the order of the eruption<sup>202</sup> occasionally with a light dusty desquamation and faint pigmentation.<sup>203</sup> The face and neck may be cleared while the legs are still red.



Fig. 43.—German measles. Post-irritative lymphatic nodes. (Courtesy Dr. Max Fox.)

The pharynx is diffusely red and the tongue often resembles the raspberry tongue of scarlet fever; that is, it is diffusely red, not coated and the fungiform papillae are swollen.

### Roseola Infantum (Exanthema Subitum)

John Zahorsky<sup>212-27</sup> of St. Louis (in 1910 to 1913) separated from various little-understood exanthematic diseases of childhood a typical entity to which he unfortunately gave the old name of roseola infantum. The term erythema

<sup>212</sup>Zahorsky J. Roseola Infantum. Survey of Literature. Arch. Pediat. 27: 403-409, 1910.

<sup>213</sup>Zahorsky J. Roseola Infantum. In J. Breckenmann, Practice of Pediatrics, ed. 11. Harewood, Md., 1937. W. F. Prior Company, Inc.

subitum<sup>373</sup> has become more popular while Glanzmann's<sup>348</sup> unwieldy name "critical three days fever exanthem of the infant" is used only rarely.

The disease is an acute infection which at least in some countries attacks a large percentage of the infants. Rosenbusch<sup>376</sup> estimates that about 50 per cent of the young children become infected mostly at the end of the first year of life, rarely after the third year.

The etiology is unknown but influenza has been suspected.<sup>377</sup> The incubation period is seven days (from five to fifteen days, Sobel<sup>44</sup>). Lasting immunity results from the infection but a few cases of repeated attacks have been observed.<sup>378-379</sup> About 40 per cent of the cases occur in summer and only 18 per cent in winter.<sup>373</sup>

The clinical picture is characterized by three days of continuous high fever and the eruption of a morbilliform rash immediately after the critical end of the fever. The onset is sudden sometimes alarming with convulsions<sup>380</sup> headache and vomiting. Sometimes however the children do not complain in spite of the fever. Complications are almost unknown and in many cases the general well being is not disturbed. Coryza and other mucosal symptoms and adenopathy are mild. There is a characteristic drop of the polymorphonuclear leukocytes (2 to 20 per cent) and a relative lymphocytosis and mononucleosis (80 to 98 per cent).<sup>381</sup> These findings are most marked on the third day.<sup>71</sup> The spleen is not enlarged. The prognosis is invariably favorable in spite of the sometimes alarming onset.

**Dermadromes.**—The rash appears as Glanzmann<sup>344</sup> poetically puts it as the aurora of recovery after the fever period. It starts on the back and covers the trunk within twelve hours sometimes leaving the face the scalp and the extremities free. A second crop may then cover the limbs and remain visible when the first eruption has faded. The rash consists of slightly raised rose spots from 2 to 5 mm. in size confluent or in irregular groups between which are small areas of normal skin. Later a large confluent erythema may appear on the back suggesting scarlet fever. There is no pruritus and the rash disappears in two or three days without pigmentation or desquamation. There is no characteristic enanthem an important differential feature.

The diagnosis may be difficult, especially in isolated cases. The most important feature is the eruption at, or after the fall of the temperature on the fourth day. In measles the rash appears at the height of the disease the whole syndrome is more severe and infections among siblings are common. In scarlet fever there is sore throat a typical tongue the exanthem appears early and

<sup>373</sup>Veeder R. R. and Hempelmann, T. C. Exanthem Subitum. J. A. M. A. 77: 87-1726, 1921.

<sup>374</sup>Rosenbusch H. Exanthema Subitum. Schweiz. med. Wchnsch. 66: 1172-75, 1920.

<sup>375</sup>Opila, H. Masern, Exanthema subitum. Kinderärzt. Praxis. 6-8, 1920.

<sup>376</sup>Hareberg L. H. and Greenough, L. Exanthema Subitum. Am. J. Dis. Child. 58: 952-983.

<sup>377</sup>Rever H. H. J. Roskola Infantum. New York Stat. J. Med. 41: 1884-1892, 1941.

<sup>378</sup>Greenhalgh, H. N. Roskola Infantum. Wisconsin M. J. 46: 25-27, 1941.

lasts much longer and there is desquamation and leukocytosis. Rubella which may look very much like roseola infantum has the characteristic lymphadenopathy. Erythema infectiosum rarely causes fever and the exanthem starts on the face especially over the bridge of the nose. Drug eruptions and toxic and infectious erythemas must be considered. No specific therapy is known.

### Erythema Infectiosum

Erythema infectiosum which is also known under a number of other names, for example fifth disease and megalerythema is a moderately contagious infection of unknown cause usually affecting children. The disease occurs in epidemics of relatively small size often in institutions. The outbreaks are usually in late winter and spring. Animal inoculation and bacteriological studies have not been successful. However children have been infected by injection of blood taken at the height of the rash and by pharyngeal mucus.<sup>32</sup>

The incubation period is about nine to fourteen days but it was only twenty four hours in the experimental infections. There are no or very slight prodromes. The disease starts suddenly with a *rash* which is the main and sometimes the only symptom. The exanthem appears first on the face as small red spots which soon grow and coalesce forming an erythema which is most pronounced over the cheeks and which leaves the perioral and periorcular areas pale. The erythemas of the cheeks are often connected by a red isthmus over the base of the nose so that a butterfly figure results. The erythema is usually bright red<sup>33</sup> sometimes pink or cyanotic<sup>34</sup> the fairly well-defined edges are slightly palpable and raised and the surface is smooth and in severe cases hot to the touch. The chin is seldom affected the forehead is more often affected. The patient looks as if he has been slapped on both cheeks so definite is the erythema.<sup>35</sup>

One to two days later the erythema usually appears on the outer surfaces of the upper arms and sometimes on the buttocks and extensor aspects of the thighs.<sup>36-38</sup> The lesions are slightly papular and have a tendency to grow peripherally and to fade in the center. Thus ring-shaped garlandlike zigzag lattice<sup>39</sup> honeycomb and other patterns result. The hands and feet are not affected. There is only slight fever no enanthem and little itching. From the third to the twelfth day the eruption fades but relapses may occur up to several months later. Atypical rashes affecting only the limbs are rare.<sup>36,40</sup> Desquamation is usually lacking. In a small portion of the cases the face remains free.<sup>36</sup> There

<sup>32</sup>Taccone G. Sulla quinta malattia. Nuova epidemia osservata a Milano. *Pediatrica Arch. dipat. clin. pediat.* 8: 77-126 1928. *Zbl. II.* 920.

<sup>33</sup>Chargia, L. Sobel, N. and Goldstein, H. Erythema infectiosum. *Arch. Dermat. & Syph.* 47: 467-477 1943.

<sup>34</sup>Tobler L. Erythema infectiosum. *Ergebn. d. inn. Med. Kinderh.* 14: 70-85 1918.

<sup>35</sup>Romero Leraas A. Erythema infectiosum. *Pediatrica scop.* 23: 207-220 1924. *Zbl. II.* 13.

<sup>36</sup>Klimmer F. Erythema infectiosum. *München med. Wchnsch.* 1929. II: 1281.

<sup>37</sup>Lawton, A. L. and Smith, H. E. Erythema infectiosum. *Epidermo. Arch. int. Med.* 47: 23-41 1931.

<sup>38</sup>Rector J. M. Erythema infectiosum—Clinical Observations. *J. Pediat.* 18: 246-245, 1929.

is moderate lymphocytosis and eosinophilia of 6 to 11 per cent<sup>364-365</sup> (Zikowsky<sup>366</sup> 20 per cent) during convalescence and later mononucleosis. Lymphadenopathy is uncertain. The children twice as many girls as boys<sup>367</sup> are but little disturbed. Complications are hardly ever seen and fatalities have not occurred.

### Febris Herpetica Febris Ephemera, Febricula

Febris herpetica febris ephemera, and febricula comprise a group of fevers of unknown etiology characterized by a high temperature for about one day with the usual complaints of an acute febrile disease. In many of these short fevers *herpes labialis* appears usually with sinking temperature or one or several days after the bout.<sup>368</sup>

### Rubeola Scarlatinosa, or Fourth Disease, Dukas Filatow Disease.

Rubeola scarlatinosa is also called fourth disease and Dukas-Filatow disease. There is much objection<sup>369</sup> to the acknowledgment as an entity of a febrile exanthem of which a few small epidemics have been observed.

After an incubation period of from nine to twenty days that is much longer than in scarlet fever the disease starts with a pink, scarlatiniform slightly papular exanthem which covers the body within a few hours and does not always leave the circumoral area free. The face is generally less involved than the other parts. The rash fades after one to three days and is followed by a slight branny desquamation. The pharynx is red and the tongue only slightly coated.

The fever is mild and does not last longer than the rash. There are no important complications.<sup>370</sup> There is no cross-immunity with scarlet fever the mild cases of which the disease resembles.

### Miliary Fever (Sweating Sickness)

About 200 epidemics of miliary fever or sweating sickness have been described since the first outbreak frightened London in 1486<sup>371</sup>. No sporadic or endemic cases have been observed. The epidemics usually occurred in spring or summer in an explosive form commonly restricted to relatively small areas like cities or valleys. The mortality of the epidemics varied from 11 to 90 per cent with an average of 8 per cent in the nineteenth century. This is a greater fluctuation than is known of any other epidemic disease. The horror caused by the high mortality of some of these epidemics was augmented by the sudden outbreak and the fulminating course. Frequently persons who had been in good health died within one or two days. More recently epidemics have occurred

<sup>364</sup>Yarrell, O. *Erkrankheiten und Blutdiagnostik*, ed. 8 Berlin 1931, Julius Springer.

<sup>365</sup>Zikowsky J. *Erythema infectiosum* Wien klin. Wochenschr. 1932, II 843-847.

<sup>366</sup>Willrich, O. *Febris herpetica* Vienna, 903 Alfred Hölder.

<sup>367</sup>Willrich, A. *Der Priesel, vom historisch- und geographisch-pathologischen Standpunkt* Virchow Arch. f. path. Anat. 9 484-523 1885 9 126-171, 1886.

in France<sup>292</sup> and Southern Germany and perhaps in Rumania<sup>293</sup>. The last certain outbreak was observed in some French hamlets by L. Rousseau<sup>292</sup> in 1926 with hardly any variations from the classic picture. No epidemics have become known in America.<sup>294</sup> The cause of the infection is unknown. The incubation period<sup>291, 294</sup> seldom exceeds one to two days but was found to be from ten to fifteen days in the cases of Stroë and Stroë<sup>295</sup>. Prodromes are either entirely lacking or consist of sudden weakness, malaise and muscular pains. The onset is abrupt occurring frequently at night. A patient going to bed apparently in good health may awake with a chill, bathed in sweat and feeling deadly sick. Precordial oppression, a gripping dyspnea, nausea and muscular cramps together with premonitions of death constitute acute attacks which follow each other rather frequently and in increasing strength. At the height of such a paroxysm death may occur.

The spleen is enlarged. The urine secretion is small even to the degree of complete anuria. Delirium is common. The fever is usually high and remittent in type.

The convalescence is slow and relapses may occur. Immunity is not certain. Mild cases occur but adults are more severely affected than children. The pathological findings are unrevealing. The content of the vesicles is not sweat but a serous exudate. No specific therapy is known.

**Dermadromes.**—The outstanding symptom after which the disease has been named is the excessive sweating (Timmermann<sup>296</sup>) which in contrast to sweats in other fevers starts with the rising temperature and continues throughout the duration of the fever. The sweating is so profuse that it is impossible to keep the patient even fairly dry by the most frequent changes of linen. The sweat is supposed to have a musty odor. After three to four days the characteristic rash appears. However many patients die before reaching the exanthematic second stage of the infection. The rash usually starts as a slightly papular eruption on the neck and chest and spreads in several crops over the whole body. The forehead and scalp are heavily affected and the face the least.<sup>292</sup>

The individual lesion is a red papule or macule with a central acuminate vesicle which is at first yellowish and clear but after one to two days is opaque. The exanthem may at times, especially in children, be quite morbilliform but confluent scarlatiniform and hemorrhagic varieties have been seen in some epidemics.<sup>292</sup> The vesicles dry and crust after two to three days and heal with a branny or flaky desquamation. Oral lesions look like aphthae. The eruption is preceded by formication or tingling and accompanied by a feeling of relief.

<sup>292</sup>Rousseau, L. La peste millaire dans le Mont morillonais. Bull. Acad. d. med. Paris 112: 293-302, 1925.

<sup>293</sup>Stroë, A. and Stroë, H. Die Kinderschwefelpestkrankheit. Arch. f. Kinderh. 26: 78-89, 1921.

<sup>294</sup>Timmermann, H. Der Schwefelpest. Vienna, 1908, Alfred Holder.

## Onyali

Among the natives of West Central Africa occurs an acute febrile disease called onyali the main feature of which is a mucocutaneous eruption of hemorrhagic bullae. These lesions are usually found inside the cheek on the tongue and on the palate although bleeding may occur from all mucous membranes. There may also be localized hemorrhagic lesions of the skin. These blood blisters are umbilicated trabeculated and filled with loosely coagulated blood. The disease may show all the features of a severe thrombocytopenic purpura.

Severe anemia icterus bronchopneumonia and central nervous system involvement are frequent. The mortality is high. There is profound thrombocytopenia with prolonged bleeding time normal coagulation time imperfect clot retraction and a positive tourniquet test. The intramuscular injection of whole blood is said to be a good method of treatment.<sup>140</sup>

## Glandular Fever (Infectious Mononucleosis)

Glandular fever (E. Pfeiffer<sup>141</sup>) or infectious mononucleosis is a contagious febrile disease of unknown etiology characterized by generalized lymphadenopathy splenomegaly and lymphocytosis. The incubation period is usually seven days. The terms glandular fever or prolonged fever<sup>142</sup> of pharyngotonsillitis thoracic abdominal nervous septic, and other types characterize the great variability of the disease. The prognosis is good.<sup>143-144</sup>

Dermadromes.—E. Pfeiffer<sup>145</sup> emphasized the absence of exanthems, and Glanzmann<sup>146</sup> in his monograph on lymphemoid glandular fever elaborates on the lack of a characteristic rash. Other authors,<sup>147</sup> however have occasionally or frequently<sup>148-149</sup> seen erythema multiforme and lichenoid morbilliform diffuse erythematous maculopapular rose spot-like or very rarely purpuric exanthema. The rashes appeared during the first two weeks.

The epidemic in London in 1930 was marked by unusually frequent typhoid-like rose spots which appeared before the lymphadenopathy. Recently a rash incidence of 14 per cent has been reported (Minkenhof after Robert<sup>150</sup>). The blood count remains indispensable for the diagnosis. Of importance is the velvety red appearance of the gums which bleed easily. In severe cases the teeth may submerge in these fragile tissues. On other parts of the oral mucosa especially on the soft palate small grouped papules may appear and cause a granulated appearance. On such infiltrations shallow small or larger punched-out aphthous ulcerations may develop. Slight follicular and severe diphtheroid and

<sup>141</sup> Pfeiffer E. Onyali. Roy Soc Trop Med & Hyg 25: 207-220 1937

<sup>142</sup> Pfeiffer E. Das Drüsenglied. Verhandlungen deutscher Katarforscherversam. 1930

<sup>143</sup> Wylie H L. Glandular Fever and Infectious Mononucleosis. Lancet 1934 II 140-234

<sup>144</sup> Glanzmann E. Das lymphemoid Drüsenglied. New York 1930. 8 Kap.

<sup>145</sup> Lebedeff H and Schwarz E. Das Drüsenglied. Ernste d. inn. Med u. Kinderh 62: 775-776 1903

<sup>146</sup> Glanzmann E. The Skin Eruption and False-Pockles Characteristic in Infectious Mononucleosis (Glandular Fever). J. Derm. (Chn) 2: 230 1941

<sup>147</sup> Glanzmann E. Die Hauteruption und False-Pockles Charakteristisch in Infectious Mononucleosis (Glandular Fever). J. Derm. (Chn) 2: 230 1941



ulcerative tonsillitis have often been reported. The oral ulcerations appear after the swelling of the submaxillary lymph nodes.

Unilateral *conjunctivitis* of a dry granular character is not rare.<sup>439</sup> In exanthematic cases the Wassermann and Kahn reactions may temporarily become positive.<sup>440</sup>

### Foot and Mouth Disease (Apthous Fever)

Although the foot and mouth disease (aphthous fever) is predominantly an epidemic infection of cattle and other cloven hoofed animals it is occasionally transferred to man by contact with infected animals or drinking of their milk. The cause is a filtrable virus.

In man the infection has an incubation period of two days. The onset is sudden with fever headache and malaise. On the following day salivation and an *eruption* of many umbilicated vesicles on the buccal and labial mucosa appear the lesions being surrounded by a bright red areola. The tongue and the pharynx may be similarly involved. On the third or fourth day the disease enters a second stage.<sup>441</sup> New grayish or yellowish vesicles and larger blisters with or without red areolae may cover the hands and feet and even the legs.<sup>442</sup> The nail beds are often mentioned as the site of troublesome inflammations. The nails may be shed or they may show transverse grooves. Maculopapular multiform and varicelliform exanthema involving the entire skin or much of it have been described.<sup>443-444</sup> The mouth condition together with diarrhea rhinitis and conjunctivitis and the symptoms of general infection may cause an alarming picture. Around the fifth day the symptoms subside and after ten days or more the patient is usually cured.<sup>445</sup> The prognosis is good although some deaths have been reported. The treatment is symptomatic.

The identity of human and animal infection has been corroborated by successful inoculation of human material into cattle<sup>446</sup> and guinea pigs.<sup>447-448</sup>

### Dengue Fever

Dengue fever is an acute nonfatal widely distributed febrile disease of the warm climates. It is transmitted by various mosquitoes including *Aedes aegypti* the carrier of yellow fever. The cause is a filtrable virus.<sup>449</sup> The incubation period is about seven days.<sup>\*</sup>

<sup>441</sup>Von Schick, L. Maul- und Klaueneruption beim Menschen. Klin. Wochenschr. 1: 630-632, 1921.

<sup>442</sup>Virena, L. 2 Fälle von Maul- und Klaueneruption beim Menschen. Berl. (Berlinal) Wochenschr. 27: 231, 1921.

<sup>443</sup>Gibson, A. H. A Case of Foot-and-Mouth Disease. Lancet 1924 I: 432.

<sup>444</sup>Tappiner, S. Maul- und Klaueneruption beim Menschen. Arch. f. Dermat. u. Syph. 136: 180-201, 1940.

<sup>445</sup>Geriach. Maul- und Klaueneruption beim Menschen und Übertragung auf Meerschweinchen. Wien. klin. Wochenschr. 27: 210, 1924.

<sup>446</sup>Berziarelli. Übertragung der Maul- und Klaueneruption auf den Menschen und Wiederimpfung der menschlichen Krankheit auf die Rinder. Zbl. f. Bakteriol. 48: 625, 1907.

<sup>447</sup>Waldmann, H. and Page, J. Experimentelle Untersuchungen über Maul- und Klaueneruption. Berl. (Berlinal) Wochenschr. 27: 240-244, 1921.

<sup>448</sup>Ullrichoth, P. Übertragung der Maul- und Klaueneruption auf Meerschweinchen. Deutsche med. Wochenschr. 47: 671-672, 1921.

<sup>449</sup>Simmons, T. R. Dengue. N. Clin. North America 27: 606-621, 1932.

<sup>450</sup>Kilmer, P. and Lissak, E. T. Dengue. Ann. N. Y. Acad. Sci. 20: 41-51, 1944.

The disease starts with severe frontal headache and pain in the lower back in joints and in muscles. Chills are marked and indolent lymphatic nodes are palpable over the posterior scalenus muscles<sup>41</sup>. There is bradycardia in spite of the high fever and leukopenia with a shift to the left. The temperature falls to normal on the third day but fever often returns after one to two days (saddle-back curve). The second fever is sometimes higher and ends by crisis around the seventh day. Deaths are very rare but convalescence may drag out over several weeks. No specific laboratory test nor treatment has been developed.

**Dermadromes.**—The initial fever is often (38 per cent Simmons<sup>44a</sup>) accompanied by an erythematous symmetric rash or extensive flushing which is most pronounced on the face neck chest forearms and palms<sup>42</sup>. The eyes are reddened also. This flushing is out of proportion to the temperature and was seen in about 26 per cent of the cases during a recent major epidemic.<sup>43</sup> The flushing subsides gradually. If there was any erythema of the chest it may be converted into the secondary rash which does not involve the face. This secondary or terminal exanthem was seen more often (37 per cent Kistner and Linnakv<sup>41</sup> 86 per cent, Simmons<sup>44a</sup>). It appears between the second and sixth days and is macular occasionally maculopapular scarlatiniform or rarely hemorrhagic. It usually starts on the chest, back or abdomen and spreads to the trunk but this sequence may be reversed if the rash starts later in the illness. No definite relationship seems to exist between the onset of the second fever attack and the terminal rash which is followed by an imperfect desquamation and itching of the palms and soles.<sup>44b</sup>

Some authors emphasize the sweating and the variability of the rashes.<sup>45</sup> Complicating pyodermatoses are common.<sup>4</sup>

**Pretibial fever.** An epidemic febrile illness of approximately five days duration characterized by slight respiratory symptoms headache leukopenia palpable spleen and a symmetrical maculopapular rash mainly over both pretibial areas, vaguely resembling erythema nodosum has been observed among troops in South Carolina.<sup>4</sup> The rash was present in 80 per cent of the forty cases. All efforts to determine the nature of this pretibial fever were in vain.

### Phlebotomus Fever

Phlebotomus, papatasi or sandfly fever is a benign sandfly-borne virus infection of hot and dry countries, characterized by a fever of two to four days duration severe frontal headache and eye-ache photophobia and muscular pains. There is leukopenia and shift to the left. The face is described as cur-

<sup>41</sup>Stewart, P. H. Dengue, U. S. N. M. Bull. 42: 1333-1476, 1944.

<sup>42</sup>Almeida, L. Yellow Fever and Dengue. J. Pediat. 23: 618-617, 1932.

<sup>43</sup>Lincoln, H. Beobachtungen bei einer Epidemie von Dengue Fieber mit mannigfaltigen Symptomen. Acta dermat. 36: 43-46, 1932. Zbl. 48: 221.

<sup>44</sup>Dracoulides, N. Observations dermatologiques au cours de la dengue (pendant la pandémie d'Athènes, en 1928). Bull. Soc. franç. de dermat. et syph. 36: 612-618, 1929.

<sup>45</sup>Dunbar, W. B. and Gorman, H. A. Pretibial Fever an Obscure Disease. J. A. M. A. 123: 841

only red and puffy in contrast to the body <sup>46,47</sup> and may stay so for weeks after the fever. The conjunctivae are red and there is photophobia. Crops of vesicles at the junction of the hard and soft palates <sup>46</sup> (not seen by other observers) and probably only in a minority of the cases purpuric scarlatiniform morbilliform urticarial and erythema multiforme-like evanescent rashes <sup>47</sup> and perifollicular erythema in the axillae and about the elbows and knees have been mentioned. Herpes is not a feature <sup>48-50</sup> but occurs occasionally <sup>47</sup> in severe and atypical fashion.

Bullous reactions and severe edema following sandfly bites after convalescence are interpreted as allergic reactions. <sup>417</sup>

<sup>46</sup>Walker A. B. and Dods L. Epidemic of Sandfly Fever in Palestine During 1940. *M. J. Australia* 23: 345-349 1941.

<sup>47</sup>Marchionni A. Haut und Schleimhauterscheinungen beim Pappatacifeber in Amasien. *Arch. f. Dermat. u. Syph.* 182: 613-651 1942.

<sup>48</sup>Schilling, O. Pappatacifeber. *Handbuch der inneren Medizin*, vol. I Berlin 1935, J. F. Springer.

<sup>49</sup>Watts A. B. Philip, O. B. and Paul, J. R. Phlebotomus (Pappatacior Sandfly) Fever. *J. A.M.A.* 128: 693-700 1944.

## CHAPTER V<sup>N</sup>

### SYSTEMIC INFECTIONS<sup>N</sup>

#### Varicella (Chicken Pox)

In 1931 Texner<sup>60</sup> in a comprehensive review of the subject stated that the causative agent of varicella (chicken pox) has often been searched for and almost as often found. This is a witty overstatement. We know that it is a dermatropic, probably filtrable virus related to but not identical with Puschen's elementary bodies which cause variola and vaccinia. Injection of the content of the vesicular lesions of chicken pox into the rabbit's cornea produces within twenty four hours a small vesicle which bursts after seventy two hours. The microscopic picture of the cornea is quite characteristic especially the giant cells with large eosinophile inclusions found by Gins (see Texner<sup>60</sup>). Tysner (after Lipschütz<sup>61</sup>) found nuclear inclusions which Lipschütz<sup>61-62</sup> believed to be microscopically identical with the inclusions found in herpes zoster (zoster bodies).

The virus is contained in the skin lesions and probably in the blood stream. Experimental skin infection with nasal mucus has been as unsuccessful as the infection of the tonsils with vesicular fluid but the intradermal inoculation of blister serum produces after nine days a typical vesicle which always remains localized and can be successfully used for further inoculations. The inoculation is unsuccessful in persons who have had varicella. It immunizes against chicken pox with considerable reliability<sup>63</sup>.

Droplet infection through the lungs seems to be the most important way of contagion. Indirect transfer is negligible.

Chicken pox is endemic and epidemic usually affecting children. Varicella has a good prognosis unless one of the rare complications occurs. Newborn infants and adults are much less frequently but usually more severely affected<sup>64-65</sup>. The infection is followed by long lasting immunity.

The incubation period varies from seven to twenty-six days but is usually thirteen to fourteen days. Prodromes are little marked. Fever is common especially in older children or adults and convulsions, sleepiness, photophobia and gastrointestinal symptoms may occur. Very short lived prodromal or initial rashes are not common (1 per cent). They are mostly scarlatiniform rarely

<sup>60</sup>Texner O. Varicellen, Ergänz d. inn. Med. Klin. 41: 243-252, 1931.

<sup>61</sup>Lipschütz B. Die Ektoschleimkrankheiten der Haut, Handb. d. H. Gk. 2: 31-164, 1932.

<sup>62</sup>Lipschütz B. and Kaudratis, K. Über die Ätiologie des Roster und über seine Beziehungen zu Varicellen. Wien. klin. Wchnschr. 23: 499-503, 1925.

<sup>63</sup>Greenhalgh, R. M. Prophylaxis of Varicella With Vesicle Fluid, Am. J. Dis. Child. 21: 541-545, 1926.

<sup>64</sup>Waring, J. J. Neuburger, K. and Geever, E. F. Chickenpox, Severe Form in Adults, Arch. Med. 63: 254-409, 1942.

<sup>65</sup>Leber, Karl. Über Varicella bei Erwachsenen, Leipzig, 1921. Dissertation.

morbilliform or polymorphic and seem to forecast a more severe course. Giant cell formation in the tonsils similar to that seen in measles has been found in chicken pox during the prodromal stage.<sup>48</sup> All symptoms may be absent and the exanthem may break out with the patient in apparently good health. This conspicuous lack of sick feeling often causes the child with varicella to be brought to the office of the dermatologist because the idea of a systemic infection does not enter the mother's mind. This rarely happens in the other important exanthematic diseases of children.



FIG. 43.—Varicella. (Courtesy Dr. St. Fox.)

**Dermadromes.**—The eruption starts on the face and on the scalp, that on the body (back) being only slightly later, though some isolated vesicles may precede the main eruption. The distribution of the exanthem, which may develop fully in one to two days, is most dense on the trunk and becomes lighter toward the extremities and the acra. This centripetal tendency is in marked contrast to the centrifugal distribution of the variola pustules, which leave the trunk and especially the abdomen relatively free and crowd on the hands and feet. The individual lesion appears as a small macule which in twenty-four hours develops into a clear vesicle which is often surrounded by a relatively wide bright red areola. The blister is sometimes oblong, rarely pustular or hemorrhagic. Pri

<sup>48</sup>Toddinson, T. H. Chickenpox: Giant Cell Form in Prodromal Stage. *Am. J. Pa. h.* 18: 523-526 1929.

many umbilication of the filled lesions is rare though early rupture, depression and formation of a sunken crust in the center may suggest umbilication but should not be taken as such. The vesicle is multilocular, but the septa as well as the wall are much thinner than in small pox so that the lesion often can be "wiped off" with a rough towel. The blister is quickly followed by a crust which



Fig. 44.—DuRoiis and hemorrhagic rubelespon. (Courtesy of Division of Dermatology, Department of Medicine, University of Chicago.)

may adhere for many days or as long as two weeks. A few larger and deeper lesions may leave pitted scars with pigmented margins but the marks are rarely disfiguring. The lesions are more numerous on irritated or macerated skin. The exanthema vary in density from a few lesions to a copious eruption of many hundreds of efflorescences, in all stages of development. This latter peculiarity is due to the appearance of successive crops and to the fact that the individual lesion may become arrested in any stage of development. The crops may be

accompanied by mild fever. After one week the crops stop appearing although miliary like weak eruptions may continue to follow. The last eruptions are mild and the lesions usually fail to mature to vesicles.

There are several *clinical varieties* of chicken pox and its complications.<sup>49-51</sup> The eruption may form bullous, impetiginous or coalescent lesions. Confluence indicates a severe infection.



Fig. 43.—Varicella gangrenosa. Fatal case. (Courtesy Dr. Max Fox.)

*Varicella pemphigodes* is a rare variety characterized by large flaccid bullae with adherent centers. Such cases may be accompanied by high spiking temperatures<sup>52</sup> and has repeatedly taken a fatal course.<sup>53</sup> Some of these cases seem to be a combination of varicella and secondary pyogenic infection. Erysipelas is a dangerous complication. In some cases the vesicles remain very small; this is called *miliaria varicellosa*.

In *varicella gangrenosa* the normally fast sequence of drying and crusting of the vesicles is disturbed by a progressive necrosis which leads to punched-out gangrenous ulcers. The floor of these ulcers is covered with necrotic greenish material. Hemorrhagic features are common so that the ulcers often appear black. However, an occasional black discoloration of the otherwise normal crusts does not warrant the diagnosis of gangrenous chicken pox. Several ulcers may coalesce so that palm-sized gangrenous defects ensue which may even lay bare the underlying muscles. In some instances the gangrene started in apparently normal skin and not from the vesicles.

<sup>49</sup>Roushleben G. W. and Kelleher W. H. Chickenpox, Atypical Forms. *Bull. J. Child Dis.* 23: 23-24, 1925.

<sup>50</sup>Schwartzman J. Varicella and Pemphigus. *Ann. Arch. Pediatr.* 57: 895-899, 1910.

Gangrenous varicella is a severe disease with high temperature prostration and often fatal course. Infants and sick youngsters are more likely to develop this complication than older and otherwise healthy children. Scarlet fever, diphtheria, and tuberculosis are among the predisposing diseases. Banks and McCartney<sup>43</sup> in a fulminating case of massive skin gangrene in the eruptive stage of varicella, found streptococci to be the causative organism. Hemolytic streptococci are also the cause of dangerous cellulitis and of erysipelas and lymphadenitis. Infected lymph nodes usually break down and form abscesses. Cutaneous complications amount to 57 per cent of all the complications of chicken pox.<sup>44</sup> The incidence of gangrenous varicella amounts to about 1 per cent,<sup>45</sup> but seems to be much smaller in the United States. More than one half of the reported cases of gangrenous varicella ended fatally.



Fig. 46—Hemorrhagic and unusually copious varicella. (Courtesy Dr. Max Fox.)

Knoepfelmacher<sup>46</sup> separates from other purpuric manifestations in varicella the prodromal purpura and the purpura which occurs not too infrequently in mixed infection of pertussis and varicella. The varicella eruption is rarely hemorrhagic from the start. The vesicle content may become bloody or there may be other purpuric features. The whole syndrome of thrombocytopenic purpura<sup>47</sup> may develop during or after the infection in rare instances together

<sup>43</sup>Banks, H. S. and McCartney, J. E. Varicella Gangrenosa Due Streptococcus Pyogenes, *Lancet* 1937 II 311-314.

<sup>44</sup>Radewa, J. O. M. and White, S. M. Complications of Varicella. Their Occurrence Among 2,524 Patients, *Am. J. Dis. Child.* 49 923-926 937-932 1932.

<sup>45</sup>Knoepfelmacher. *Varicellen und Hautblutungen* Wien med. Wochenschr. 1916, p. 940.

<sup>46</sup>Olsen, H. J. Acute Thrombocytopenic Purpura Following Varicella, *Arch. Pediat.* 37 773-776, 1930.



with massive skin gangrene.<sup>42</sup> Pyogenic sepsis has been blamed in some of these cases.<sup>43</sup>

The diagnosis of chicken pox is only difficult in unusual types, in isolated cases, or in times of a smallpox epidemic. Many authors discuss the differential diagnosis of chicken pox and smallpox<sup>44-46</sup> (Tièche after Texner<sup>45</sup>). The most important points are. In chicken pox as compared with smallpox, the prodromes especially fever are mild or lacking. The distribution of the rash is centripetal starting and massed on the trunk. It appears in crops, and the lesions show different stages of maturity. The lesion is generally less round and less firm so that it can be wiped off and it is rarely umbilicated. The halo (corona) is more irregular wider and it develops faster. These criteria should all be taken with a grain of salt and the diagnosis should not rest on any one sign or symptom. (See also under Variola.)

No specific laboratory test for chicken pox has come into general use so that a negative Pauli test for smallpox may in certain cases, become an important diagnostic aid.

Occasionally *Kaposi's varicelliform eruption* a rare acute vesiculopustular eruption with severe systemic reactions may have to be considered. In most of the known cases the rash was superimposed on atopic dermatitis. The umbilicated lesions resemble vaccinia more than varicella but they appear in crops and the Paul test is negative. There is increasing evidence that the disease is a generalized herpes infection.<sup>46-49</sup>

### Herpes Zoster and Varicella

As far back as 1891 Von Bokay<sup>48</sup> published reports of five different instances of chicken pox in children following herpes zoster in a parent or other contact after a period approximately equal to the incubation period of varicella. These observations apparently easy to check were almost ignored until in 1909 the same author<sup>49</sup> presented a second series. Since then far more than 300 cases have become known and the puzzling matter continues to appear in additional publications.<sup>48-50</sup> The most common type of relationship between the two diseases is an outbreak of varicella in one or several persons who have had con-

<sup>42</sup>Steiner A T and Lockwood, W W. Varicella Complicated With Thrombocytopenic Purpura and Gangrene. *J Pediat* 12: 641-647 1937.

<sup>43</sup>Wernethoff G. Differential Diagnosis of Chickenpox and Smallpox. *New England J Med* 238: 18-19 1944.

<sup>44</sup>Laidlaw F W. Smallpox and Chickenpox. Differential Diagnosis. *New York State J Med* 28: 210-212, 1928.

<sup>45</sup>Blattner R J, Keys F M and Harrison M L K. Etiology of Kaposi Varicelliform Eruption. *J Pediat* 27: 207-3 & 1948.

<sup>46</sup>Lynch F H. Kaposi Varicelliform Eruption. *Arch Dermat & Syph* 51: 129-137 1945.

<sup>47</sup>Lane O W and Heydell W G. Kaposi Varicelliform Eruption. *Arch Dermat & Syph* 50: 398-404 1944.

<sup>48</sup>Evans G H, Batta T H and Steves R J. Kaposi Varicelliform Eruption. *Arch Dermat & Syph* 51: 134-135, 1945.

<sup>49</sup>Von Bokay J. Ueber den aetiologischen Zusammenhang der Varicellen mit gewissen Fällen von Herpes Zoster. *Wiener klin Wochenschr* 1909 p 1223. *Jahrb f Kinderh* 106: 8-23 1924.

<sup>50</sup>Blatt, M L, Zeldes M and Rehn, A F. Chickenpox Following Contact With Herpes Zoster. 2 minor epidemics. *J Lab & Clin Med* 38: 9: 1-955 1950.

<sup>51</sup>Barber L P. Generalized Herpes Zoster: 8 cases. *Arch Dermat & Syph* 40: 574-596 1939.

tact with a person suffering from herpes zoster. In several instances accidental chicken pox infection from other sources could be fairly conclusively ruled out for example in Lynch's<sup>44</sup> case by the fact that the hospital where the case occurred was in quarantine for twenty-one days because of scarlet fever while the incubation period of chicken pox rarely exceeds seventeen days. Occasionally



Fig. 47.—Herpes zoster in varicella. (Courtesy of Division of Dermatology, Department of Medicine, University of Chicago.)

secondary cases of varicella developed from those varicella cases which stemmed from herpes zoster thus proving their true chicken pox nature. However these infections did not prove as highly contagious as is usual.<sup>44, 45</sup> The appearance of herpes zoster after contact with chicken pox is seven times rarer than chicken

<sup>44</sup>Lynch, F. W. Herpes Zoster and Chickenpox, Arch. Dermat. & Syph., 64: 85-90, 1911.

<sup>45</sup>Monticelli, S. L. Herpes Zoster-varicella. Bull. Soc. Ital. pediat. 3: 183-185, 1934.

pox after zoster.<sup>446</sup> Very rare too are the sequences chicken pox—herpes zoster—chicken pox or zoster—zoster—chicken pox or other alternations. Chicken pox, simultaneously with or following herpes zoster in the same person usually an elderly man, varicella with herpetiform groups of vesicles, and herpes zoster with aberrant or generalized lesions have been reported.<sup>445</sup> The cases in which



Fig. 48.—Varicella in adult. Ith herpes zoster. Same patient as in Fig. 47. (Courtesy of Division of Dermatology, Department of Medicine, University of Chicago.)

one disease followed the other have been interpreted in favor of a close relationship or identity of the diseases<sup>446</sup> as well as to prove their different nature since immunity which probably follows herpes zoster and certainly follows varicella would be more likely to prevent the sequence than to produce it.<sup>447</sup> The interpretation of the relationship between herpes zoster and varicella as a fortuitous one is refuted by the apparent lack of any co-occurrence between—for example herpes zoster and measles—which should occur just as often if coincidence were the only factor. The most interesting experimental study was made by K.

<sup>445</sup>Fleming, J. Herpes and Varicella Simultaneously in Same Patient. *Glasgow M. J.* 122: 72-73, 1939.

<sup>446</sup>Ferriman, D. G. Chickenpox and Herpes Zoster in Same Patient. *Lancet* 1926: I, 930-931.

<sup>447</sup>Schönfeld, W. Herpes Zoster and Herpes Simplex, *Handb. d. H. Gk.* 7: 1, 122, 1935.

Kundratitz<sup>44</sup> who in seventeen out of twenty-eight cases successfully inoculated herpes zoster into children who had not had chicken pox. Two of the inoculated children developed after the varicella incubation period a generalized eruption identical with varicella. The inoculation was never successful in children who had had chicken pox and those children who had been successfully inoculated with herpes zoster or who had been treated with zoster-convalescent serum proved to be immune to varicella. Lipschitz<sup>45,46</sup> found nuclear inclusion bodies



Fig. 48.—Chickenpox and herpes zoster. The chickenpox preceded the eruption by a few days (From Top, Franklin H. Handbook of Communicable Diseases, The C. V. Mosby Company.)

which he believed to be characteristic of both diseases, in the inoculation reactions of Kundratitz's<sup>44</sup> cases. Kundratitz's experiments were on the whole confirmed by Bruusgaard.<sup>47</sup> Experimental infection with varicella stemming from herpes zoster just by placing the beds of the children close together was accomplished several times by Braslavsky.<sup>48</sup> A new contribution is the finding of similar inflammatory changes in the spinal ganglia in varicella as are known to occur in

<sup>44</sup>Kundratitz K. Experimentelle Uebertragung von Herpes Zoster auf den Menschen und die Meerschweinchen. *Ann. Herpes Zoster zu Varicellen*, Monatsschr. f. Kinderh. 23: 810-822, 1923.

<sup>47</sup>Bruusgaard, E. The Vital Relation Between Zoster and Varicella, Brit. J. Dermat. 44: 1-24, 1932.

<sup>48</sup>Braslavsky, P. Herpes Zoster and Varicella, Kiev med. X. 3 and 4: 42-52, 1927; Zh. 36: 351.

herpes zoster<sup>42</sup> Some authors believe that the incidence curve of herpes zoster and varicella runs parallel

All theoretical explanations of the relationship between herpes zoster and varicella have so far remained unsatisfactory<sup>43-45, 46</sup> mainly because of varicella zoster cases in the same person. Unitarian and dualistic schools of thought have formed ranging from complete denial of any relation to close relationship with dermatotropism of the virus in varicella and neurotropism in zoster. The matter is still highly controversial<sup>42</sup> however some relationship cannot be doubted.

### Vaccinia

Vaccinia is an infection of cattle caused by a virus which seems to be identical with that of variola. Animal passage probably has modified the infection in many respects. It almost always causes a characteristic pustule at the site of infection followed only in extremely rare instances by generalized eruptions.

The disease leaves the patient immune to vaccinia and smallpox. Spontaneous infections with vaccinia are quite rare and occur mostly in dairy personnel. The intentionally produced infection with vaccinia however is one of the most common and widely studied infectious diseases of the civilized world. Though produced in order to attain a systemic effect that is immunity against variola vaccinia is usually not thought of as a systemic infection.

The first three to four days after inoculation is the symptomless incubation period. On the fourth day a raised papule (papilla) with a narrow red halo (aulla) appears. On the sixth or seventh day the papule changes into an umbilicated vesicle surrounded by a wide areola. Between the eighth and tenth days the infection is at its height and often accompanied by lymphadenopathy, fever and leukocytosis. According to some authors the spleen is palpable for a short while. The involution of the pustules starts on the eleventh day. Three to four weeks after the vaccination the local process has wound up with a scar.

The apparently solid papule appears histologically to be a vesicle with many chambers. There are characteristic vacuolizations of the cytoplasm characterized by Unna<sup>44</sup> as ballooning and reticular degenerations. The first term was chosen because of the vacuolization which finally leaves the prickle cells looking like bags filled with balls, the nuclei. The epithelial and other cells of the vesicles contain the variola vaccinia virus. Inoculation of the vesicle content into the cornea of the rabbit (Paul's test) produces in thirty-six hours characteristic epithelial papules with central crateriform necrosis. The microscopic examination demonstrates many Guarnieri bodies.<sup>44</sup> Paschen's elementary bodies can be demonstrated in smears from early lesions by staining. They resemble cocci but they are smaller.

<sup>42</sup>Dalozh E. V. Zur Lebensdauer der Windpockeneruptionen. Ein Beitrag zur Frage Varicellen und Nervensystem. Verh. B. in ernst. kong. Dermat. 2: 232-241, 1936.

<sup>43</sup>Yokawa F. J. Beobachtungen an Zoster gleichzeitig mit Variellenausbruch bei Erwachsenen. *Krankh.-Dermatologes* 79: 39-42, 1939.

<sup>44</sup>Bruns O. K. and L. Naeff H. Rille J. H. and Schönfeld, W. Beobachtungen zwischen Zoster und Varicellen. *Dermat. Wchnschr.* 1935 I: 208-214.

<sup>45</sup>Paschen E. Vaccine and Vaccinaauschläge. *Handb. d. H. Gk.* 2: 181-297, 1922.

A great number of investigations have shown that the vaccinia virus enters the blood stream and appears in the air passages, in almost all the organs<sup>63</sup> and in the secretions for example the urine.<sup>64</sup>

The blood of vaccinated children without any complications may from the third to the tenth day produce typical vaccinia in nonvaccinated children (H and K. Herzberg after Paschen)<sup>64</sup>

**Dermadromes** —In spite of the generalization of the virus which probably occurs in all cases hematogenous skin infection and development of typical lesions are extremely rare. These lesions must be separated from accidentally inoculated vaccinia on eczematous skin on the lips, on the eyes or on other susceptible parts



Fig. 60—Vaccinal rash. (Courtesy Dr. Max Fox.)

of the surface (eczema vaccinatum). True *generalized vaccinia* appears possibly after the third day but usually during the second week after the vaccination as a papular rash which passes through vesicular and pustular phases though not with the precision of the inoculated vaccinia. The eruption is disseminated sometimes universal. Exanthems are known. Sometimes the neighborhood of the original vaccination for example the same arm is especially involved. The content of the pustules produces characteristic lesions in the rabbit cornea and in the skin of nonvaccinated persons. The eruption is accompanied by moderate

<sup>63</sup>CHEN, H. A. Hackenhal, H. and Karsentown, Natalie. Neue Erfahrungen und Versuche über die Generalisierung des Vaccinavirus. *Centralbl. f. Bakteriol.* 110: 112-118, 1929. Experimentelle Untersuchungen über die Generalisierung des Vaccinavirus beim Menschen und Versuchstier. *Zentralbl. f. Bakteriol.* 110: 429-44, 1929.

<sup>64</sup>Wodnicka. Deber Vaccina generalisata und Nachweis des Virus im Urin. *Zbl. B.* 487-488.

fever and splenomegaly. The differentiation from variola and varicella may be of practical consequence. In contrast to smallpox there are no severe prodromes and no initial rash. There is no drop in temperature following the eruption. The acme is reached at the time of pustulation and is followed by slow lysis. The pustules have no areola, they are larger and they heal without scars (Drago after Paschen<sup>464</sup>). Severe varioliform cases with fatal outcome have been described<sup>467-468-469</sup>. The microscopic picture in Shortt's<sup>468</sup> case was that of



Fig. 5.—Hemorrhagic and eczematous generalized vaccinia. (Courtesy Dr. Max F. )

vaccinia. Corresponding changes were found in focal lesions of the spleen and liver<sup>469</sup>. A pemphigoid eruption of the fetus after vaccination of the mother may occur<sup>465</sup>.

Morbilliform urticarial bullous or rarely erythema multiforme-like exanthema occasionally appear during the second week, rarely earlier.

<sup>464</sup>Anders, A. E. Kuhpocken mit Stöhen. *Ann. d. Dermat. u. Syph.* 1: 161, 1919.

<sup>465</sup>Shortt, H. T. de Vere. Case of Generalized Vaccinia. *Lancet* 1923 I: 540-551.

<sup>466</sup>Al Kharrat, M. F. and Ross, R. A. Generalized Vaccinia and Eczema Vaccinat. *N. Clin. North America* 2: 753, 1933.

<sup>467</sup>Ross, H. A. *Virus and Rickettsial Diseases*. Cambridge Mass. 1930. Harvard University Press.

<sup>468</sup>Lynch, F. W. Dermatologic Conditions of the Fetus With Particular Reference Variola and Vaccinia. *Arch. Dermat. & Syph.* 28: 997-1019, 1932.

These eruptions may be analogous to the initial rashes in variola. The postvaccinal rashes have rarely been seen after revaccination.<sup>462</sup> The cause of postvaccinal rashes as well as of true generalized vaccinia is thought to be a disturbance of the antibody formation. Normally these substances are produced in sufficient quantities to neutralize the virus in the blood stream so that no exanthem appears. In other cases enough of the blood borne virus reaches the skin to cause an erythema. In the papulovesicular generalized vaccinia the antibodies are so weak or they appear so late that the virus deposited in the skin can complete a fairly normal development (Caerny and Opitz after Groth<sup>463-464</sup>).

*Hemorrhagic vaccinia* and purpura after vaccination are very rare<sup>465-467</sup> (Voigt after Paschen<sup>466</sup>). The pustules are black and they bleed; there are signs and symptoms of thrombopenic purpura. The prognosis seems favorable.

Some authors claim that the number and quality of the scars of the first vaccination indicate the degree of immunity which has been reached (Gregory after Paschen<sup>468</sup>).<sup>469</sup> In spite of great numbers of observations in revaccinated children no consensus has been reached. Armstrong<sup>470</sup> found that out of seventy one cases of postvaccination encephalitis in America seventy followed vaccination with one scratch only. It is conceivable that too little skin reaction may not produce sufficient immunity to protect against such complications.

*Psoriasis* may either develop at the site of the pustules or increased psoriatic activity and spreading may follow. While the localized eruption can be interpreted as a Koebner phenomenon (provocation of psoriasis by local irritation) the flare up and generalization of psoriasis is well known to occur after many infections.

The relation of so-called *milkers' nodules* on the hands of dairy personnel to true vaccinia is controversial.<sup>441-476</sup> Vaccination does not seem to immunize against milkers' nodules (Nagel after Robert<sup>470</sup>). Rashes similar to postvaccinal eruptions have been observed<sup>471</sup> in milkers' nodules.

<sup>462</sup>Gervais, S. Polymorphes Exanthem als Komplikation einer akkzeptierten Vakzination, *Dermat. Stchr.* 66: 240-244, 1931.

<sup>463</sup>Groth, A. Vaccines generalisata, *Abh. f. d. ges. Hyg.* 10: 665-667, 1928.

<sup>464</sup>Groth, A. Zur Ätiologie der Milcherknoten, *München. med. Wchnschr.* 75: 2122-2130, 1929.

<sup>465</sup>Paschen, E. Fall von Purpura im Anschluss an die Impfung, *München. med. Wchnschr.* 1907 p. 1901.

<sup>466</sup>Voigt, T. O. Purpura Associated With Vaccination, *Canad. M. A. J.* 63: 593-604, 1940.

<sup>467</sup>Schwartz, A. B. Postvaccinal Purpura, *Ann. Am. J. Dis. Child.* 30: 544-548, 1926.

<sup>468</sup>Kendler, H. Die Impfreaktion als Indikator der Immunität gegen Variola und Vakzine, *Verh. d. Geb. d. Med. Verwalt.* 41: 343-404, 1934.

<sup>469</sup>Armstrong, Charles. Post vaccination Encephalitis, With Special Reference to Prevention, *Pub. Health Rep.* 67: 1333-1349, 1932.

<sup>470</sup>Oppenheimer, M. and Feuler, A. Ueber Milcherknoten, *Arch. f. Dermat. Syph.* 125: 234-242, 1930.

<sup>471</sup>Kelchler, W. and Grundherr, F. J. Ueber Milcherknoten mit toxischem Exanthem, *Arch. f. Dermat. Syph.* 158: 118, 1930.

<sup>472</sup>Cherov, A. and Morozov, M. Histology of Milker' Nodes, *Sovet. vostoik. vracheb. i dermat.* 9: 315-317, 1931. *Abh.* 29: 248.

<sup>473</sup>Stark, A. H. and others. Ueber die Pathogenität der sog. Milcherknoten, *Arch. f. Dermat. Syph.* 179: 38-40, 1934.

<sup>474</sup>Woringer, F. Deux nouveaux cas de tubercules du travail, *Bull. Soc. franç. de dermat. et syph.* 41: 197-202, 1934.

<sup>475</sup>Pommal, R. J. Ueber Milcherknoten, *Dermat. Wchnschr.* 98: 124-125, 1934.

<sup>476</sup>Kren, O. Milcherknoten mit Exanthem, *Wien. klin. Wchnschr.* 21: 1831, 1930.



## Variola (Smallpox)

Smallpox is an extremely contagious usually epidemic disease. It is caused by a virus in many points identical with that of vaccinia.<sup>66-67</sup> As in vaccinia the agent is contained in the cellular inclusions found in the lesions (see vaccinia). The characteristic inclusions, Guarnieri's bodies can be demonstrated in the small grayish ulcerated papule which develops after inoculation into the rabbit's cornea (Paul's test). The disease is probably contagious even in the initial stages. The virus is spread by contact, droplets dust or contaminated persons and objects. The crusts of the healing lesions are highly contagious as are the bodies of persons who have died from the disease. Air and sunshine destroys the germs which otherwise are able to survive for a long time. The disease confers immunity although occasional reinfections have been reported. Almost all persons who neither have had smallpox nor have been vaccinated during the preceding ten years are susceptible. The fetus may become infected and be born with an exanthem or with scars.

The incubation period is twelve days with some variations and it is a rule that the shorter the incubation the severer the course. Thus, in hemorrhagic smallpox the incubation period is often only eight days while in the mild variola minor the incubation period may be twenty-one days.<sup>68</sup> The onset of the disease is abrupt. The patient is severely ill with high temperature frontal headache and intense lumbar and other muscular pain. Vomiting and constipation may be present. Delirium is common. The skin is flushed and hot. Women often start to menstruate at the outbreak of variola sometimes before the expected day. Most authors agree that severe prodromes do not necessarily usher in a severe eruption although a mild initial stage is usually followed by a mild course.

**Dermadromes.**—A peculiarity of the prodromal phase of variola is the initial rash which is observed in 15-30 per cent of the cases. It most often develops on the second day and is morbilliform or scarlatiniform rarely urticarial. The morbilliform rash starts on the face and travels within a few hours, over the body and especially over the extremities. It is most often recognizable on the sides of the body on the extensor surfaces of the extremities and on the mammae. It vanishes as quickly as it appears. Some authors<sup>69</sup> believe that the purely macular non petechial rash is of favorable prognostic significance but this is not always true.<sup>70</sup> More importance is given to the much rarer scarlatiniform rash. In this variety which may be seen on the very first day of the prodromes, the abdomen below the navel and the inner thighs are flaming red. Within this somewhat triangular shaped area (Simon's thigh triangle) petechiae can frequently be demonstrated.

In some instances similar erythemas may appear on the shoulders and on the inner aspects of the upper arms. They may be more dense on the vaccinated arm if not too much time has elapsed since the successful vaccination.<sup>67</sup> This *erythema variolosum* vanishes relatively slowly. It may still be seen in the early

<sup>66</sup>HAASTL, E. Ätiologie der Pocken. Arb. Reichsanst. Infekt. 68: 149-163, 1925.

<sup>67</sup>THOMAS, M. and JACOB, R. The Initial Exanthem of Smallpox. J. Infect. Dis. 29: 108-113, 1921.

<sup>68</sup>STODOLSKA, O. Variola, II. Inf. d. II. (Lk. 14: 1, 442, 453, 1930).

eruption period and it has often been said that the sites of the initial erythema either remain free of pocks or have relatively few. The petechiae seen in the initial rash should not be confused with the rare purpura variolosa.

The end of the third day marks the end of the initial stage and the beginning of the decisive *eruptive period*.

The *variola exanthem* appears first on the face and head. Within three days it invades the trunk and then the extremities. The face is usually the most densely covered part. Areas subject to friction as the garter and belt areas or skin which has been irritated by iodine or other irritants or the macerated folds of the groin may produce a richer crop of lesions. Face, extremities and trunk, in the order named show decreasing degrees of density. The abdomen is the

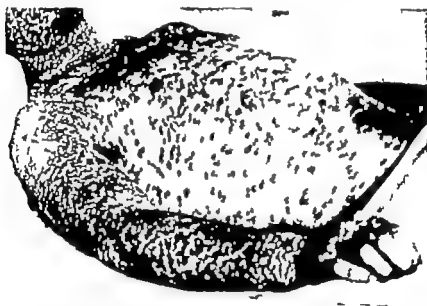


Fig. 82.—Smallpox (variola). Severe case. It is confluent rash in the face. (Courtesy Dr. M. A. Fox.)

least affected region. However, all these degrees are relative and vary widely with the severity of the case.

The individual lesion, which is accompanied by a slight burning or itching, begins as a pinhead sized papule which grows to a bright red lentil or "split-pea" sized efflorescence within one to two days. On the third day of its existence the papule develops a small vesicle on its center which within 2 or more days extends over the whole lesion. Its content changes on the fifth day from the initial clear serum to an opalescent fluid and finally to frank pus on the sixth day (ninth day of the disease). This marks the beginning of the pustular stage. The content of the vesicle is under considerable pressure, often giving the palpating finger a firm, shotty sensation. This feature, however, has been overemphasized and it may be entirely absent.<sup>20</sup> It is not possible to relieve the pressure by needle

puncture since the vesicle is multilocular. The center of many lesions becomes navel like while the edge appears raised. The pustules are surrounded by a bright red narrow halo. The skin between the pustules is often swollen.

The outbreak of the variola exanthem is accompanied by a sudden drop in temperature after which the patient feels greatly relieved. In mild cases the temperature continues to fall throughout the eruption while in the more severe cases the temperature rises again with or even before the pustulation. The maturation of the pustules takes place in the order of their appearance so that the face is always one step ahead. The duration and the severity of the pustular stage varies. While in some cases the small number and the short lifetime of the pustules may affect the general condition but little a copious or confluent



Fig. 53.—Confluent smallpox. (Courtesy Dr. Watson Campbell and Dr. C. S. Newman, from Sutton and Sutton: Diseases of the Skin, The C. V. Mosby Company.)

exanthem causes great suffering with recurrence of high temperature and delirium and all the possible complications of a highly toxic and septicemic state. Skin gangrene not related to bed sores has occasionally been observed. Most of the deaths occur in the suppurative stage. While the widespread inflammation of the skin naturally makes the patient most uncomfortable much of his suffering comes from the mucosal eruptions. The mucosal efflorescences follow the same pattern as the skin lesions: papules, vesicles, pustules. However the roof of the vesicles is destroyed early so that instead of the pustule an erosion develops. The mouth, the nasopharynx, the larynx, and even the trachea down to the bifurcation may be affected. The tonsils become ulcerated by confluent lesions. The tongue is often relatively little involved. The discomfort of the patient is not so much caused by the actual smallpox lesions on the mucosae as by the diffuse catarrhal inflammation which accompanies the exanthem. This is particularly true of the nose and nasopharynx which often are obstructed by bloody crusts.

The conjunctiva bulbi is only rarely involved the conjunctiva palpebralis a little more often. Pustules may appear usually in small numbers in the vagina the rectum and the urethra.

The pustular stage at the middle of the second week represents the acme of the disease takes a normal course. From then on the edema of the face subsides and the pus at first in the facial lesions and then in the others in the order of their appearance becomes thicker and the areolae lighter. The pustules which were firm and shotty become flat and shrink. They form yellow crusts which finally become brown dry and loose. The pain subsides however a very annoying pruritus frequently accompanies the loosening and shedding of the scabs. The respiratory irritation subsides and at the end of the second week the temperature is again normal this time to stay. The healing pustules leave pigmentations and pitted scars of varying degree. The scarring may consist of a few pockmarks not much more severe than in some cases of varicella or it may disfigure the patient's face to the utmost for the rest of his life. Diffuse alopecia follows variola probably more often than it follows other exanthematic diseases. The hair grows back except in the few spots where pustules have destroyed the hair papillae.

The clinical picture of smallpox varies considerably with the epidemic and with the status of immunity of the patient. In addition complications may modify the course decisively.

In *variola confusa* as compared with *variola discreta* the pustules are so dense that they coalesce and form large superficial abscesses and infiltrations. All symptoms are aggravated. The face is most severely involved the trunk less so. The eyes cannot be opened the lips and the nose are swollen and crusty and the saliva runs from the mouth. According to an old clinical experience (Sydenham after Osler Christian<sup>60</sup>) the number of pustules on the face decides the outcome and a relatively mild eruption on the rest of the body does not make up for a dense and confluent exanthem on the face. Such confluent cases are sometimes, but not always heralded by severe lumbar pain in the initial stage and by a precipitate eruption on the second or third day.

*Varola minor* is a mild form of variola, with a sparse exanthem which does not always start on the face.<sup>61</sup> There is no initial rash and no second fever period. All symptoms run a mitigated and abbreviated course. Tièche<sup>62</sup> often observed a one- to two-day period without symptoms between the prodromes and the eruption. Very experienced authors believe that *variola minor* is a separate disease but others<sup>63</sup> propose a unitarian theory. Some of the arguments follow. No certain case of *variola major* stemming from contact with *variola minor* is known. Vaccination does not afford the same protection against *variola minor* as against *variola major*<sup>64</sup> although this is controversial.<sup>65</sup>

<sup>60</sup>Sydenham, H. *Varola Virana*, 1896. Alfred Hölder.

<sup>61</sup>Tièche M. *Epidemiologisches und experimentelles über Variola und Vaccine*. Korresp. Schweiz. Anz. 1913.

<sup>62</sup>Sobersheim O. *Varola*. in *Monatsh. Centralbl. f. Bakteriol.* 210: 97-115. 1930, 1932.

<sup>63</sup>Van Campenhout E. *Considérations sur le diagnostic de variola major et variola minor*. Bull. Office internat. d'hyg. pub. 27: 724-17. 1931.

<sup>64</sup>Kröber F. *Beobachtungen bei einer Epidemie von Variola*. Deutsche med. Wochschr. 60: 793-794. 1934.

Variola minor does not always immunize against vaccinia (see Sobernheim). The variola minor pustule is white and has several times been described as unilocular and not umbilicated.<sup>400</sup> Such terms as *alastrim amas*, *kaffir pox*, *white pox*, and *Cuban itch* have been used to designate the epidemic variola minor. It should be emphasized that if the mild character of a case of variola is due to the status of immunity for example preceding vaccination infections stemming from such cases may be severe. The exanthem may fail to appear after the prodromal symptoms. Such cases of *variola sine exanthemas* are rare usually favorable but also contagious.

*Hemorrhagic complications* may create two distinct varieties of smallpox. If purpuric symptoms appear in the prodromal stage. If the initial rash is purpuric or petechial or if the mucosae show early petechiae or bleeding one speaks of *purpura variolosa* or hemorrhagic smallpox. These patients die within a few days in some instances before the outbreak of the exanthem. Fulminating purpura discoloring wide areas may develop. All who have seen such cases of black smallpox have been impressed by the ghastly appearance of the patient whose entire skin may be deep purple the face swollen the conjunctivae deep red and the gums bleeding.

The term *variola pustulosa hemorrhagica* characterizes the cases with the appearance of hemorrhagic symptoms in the pustular stage. This too is a severe and usually fatal complication. At first the halos then the pustules themselves become hemorrhagic. Osler<sup>401</sup> and other clinicians who have witnessed great epidemics of smallpox agree that the earlier the purpuric complications set in the more dangerous they are.

The earlier clinicians<sup>402</sup> mention two rare peculiar cutaneous variations of the healing process. Sometimes a warty-looking crusty greasy mass may remain in the place of the pustule and only slowly become eliminated. This is called wart-pox *variola verrucosa*. Still rarer is *variola siliquosa*. Here the content of the pustules disappears rapidly leaving for a while an air filled blister. The gross pathology of the inner organs shows a surprising paucity of changes. The histopathology of the early stages of the variola papule shows acanthosis with vacuolization and liquefaction around a center in the higher strata of the prickle-cell layer. Here the multilocular vesicle develops. The umbilication is caused by acanthosis which raises the edges higher than the liquefied center. The navel may disappear if the chambers of the vesicle coalesce or become more distended. The peculiar cell changes, described by Unna are identical with those in vaccinia (see under vaccinia).

The diagnosis is occasionally difficult. A secondary syphilid may though rarely imitate variola and one should search for other syphilitic signs or symptoms. Variola if modified by vaccination may resemble varicella. However chicken pox has no prodromes and the temperature does not drop during the eruption which appears in several crops predominantly on the trunk. The vesicle in varicella is very superficial and thin and can be wiped off while this is not possible with the deeper and more thickly walled smallpox lesion. The areola (corona) in varicella is irregular and sometimes very wide while the halo around

the variola pustule is narrow and regular. The shape of the varicella vesicle is often irregular even elongated in the body folds compared with the round circumference of the variola lesion. Deep-seated scabs on the palms are quite characteristic of smallpox. The shotty feel of variola lesions may be absent and may occasionally even be found in varicella. In smallpox the axilla often remains free while it is a favorite spot for the eruption of chicken pox.<sup>118</sup> Morawetz<sup>119</sup> mentions unusually copious eruptions of erythema multiforme as being a possible obstacle to the diagnosis. Here the emphasis of the distribution is on the extensor surfaces of the extremities not on the face. The prodromal stage the fever the contacts the preceding vaccinations and especially Paul's test the scarification of a rabbit's cornea with a needle dipped into the questionable lesion establishes the diagnosis (see vaccinia). In persons who have been sensitized by often repeated vaccination a skin test with sterilized material from the questioned eruption may be positive within four hours (Tieche after Paschen<sup>120</sup>) if the disease is vaccinia or variola.

No specific therapy is known. The treatment is symptomatic. Vaccination at the time of exposure attenuates the outbreak of variola to an attack of fever without eruption. A few days after exposure vaccination can still weaken the course but this is no longer true after the outbreak of the prodromes.

<sup>118</sup>Failey, A. Differential Points in Diagnosis of Smallpox and Chickenpox, Ohio State M. J. 24 944-960, 1928

## CHAPTER VI

### SYSTEMIC INFECTIONS

#### Pinta

Pinta (mal del pinto carate) is a tropical disease characterized by unusual pigmentary changes and caused by *Treponema carateum*. This treponema was discovered by Grau Triana and Armenteros in Habana, Cuba, in 1938. The spirochete for which at least six names exist (*Treponema herrejon*, *pactor americanae*, *pintae*, *dischromeoderma*) is demonstrable in active lesions by the dark field examination or by the same stains which are used to detect *Treponema pallidum* from which it is morphologically indistinguishable. For generations the disease was considered a mycosis. However, the absence of fungi, the high incidence of positive Wassermann and Kahn reactions (Menck <sup>60</sup> per cent, Herrejon and Pailares 100 per cent, after Pardo-Castello and Ferrer<sup>61</sup> and the rapid response to antisyphilitic treatment made a spirochetal cause of the infection appear probable. The disease is inoculable into normal and syphilitic persons but not into persons with pinta of the later stages (León y Blanco, Beerman<sup>62</sup>). It is believed that the infection takes place by contact and not by a vector. No venereal transmissions have become known. The infection conveys immunity. The disease occurs predominantly among colored races in the Latin American countries. About 600,000 sufferers are believed to live in Columbia and over 270,000 in Mexico.<sup>63</sup> A few cases have been discovered among Negroes in Chicago.<sup>64</sup>

**Dermadromes**—Mainly through the brilliant and heroic work of the Cuban dermatologists it is now known that seven to ten days after an inoculation of pinta material into the skin a minute *primary papule* with a red halo develops. Within two months this initial lesion gradually becomes an erythematous-quamous patch surrounded by satellite papules which tend to coalesce with the primary lesion. The primary patch may grow slowly to 10 to 13 cm. in diameter and finally become indistinguishable from secondary lesions (pintida, León y Blanco<sup>65</sup>).

<sup>60</sup>Menck W. Percentages of Positive Wassermann Reactions Associated with Various Diseases, Fifteenth Annual Report of the Medical Department of the United Fruit Company, New York, 1936.

<sup>61</sup>Pardo-Castello V. and Ferrer J. Pinta and mal del pinto carate. Arch. Derm. & Syph. 45: 643-664, 1943.

<sup>62</sup>León y Blanco F. Las queratosis palmares y plantares en el mal del pinto. Rev. de med. trop. y parasit. bacteriol. cit. y lab. 6: 167-184, 1940. Estudio epidermológico del mal del pinto en una pequeña aldea del estado de Guerrero, México. Rev. de med. trop. y parasit. bacteriol. cit. y lab. 6: 193-200, 1940. Las reacciones de Bordet Wassermann y Kahn en el período secundario del mal del pinto. Rev. de med. Trop. y parasit. bacteriol. cit. y lab. 6: 201-205, 1940. Nota sobre la evolución histórica de nuestras reacciones acerca del mal del pinto carate. Rev. de med. trop. y parasit. bacteriol. cit. y lab. 6: 219-203, 1940.

<sup>63</sup>Beerman H. Pinta. Etiology and Clinical. J. Am. J. Sy. 266: 6-1423, 1943.

<sup>64</sup>Fox H. A Census of Mal del Pinto in Mexico. Arch. Derm. & Syph. 81: 227-229, 1935.

<sup>65</sup>Leberthal, E. P. Pinta in the Continental United States. J. A. M. A. 122: 619-621, 1943.

which appear five to twelve months, or more, after the infection. A variety of *pintida*, characterized as trichophytoid, psoriasisform, lichenoid and eczematoid have been described. The lesions are at first pink, then red-purple and finally slate-colored, indicating the onset of the pigmentary changes which are so characteristic of the disease. The older secondary lesions often show a depressed



Fig. 84.—Pinta. Typical triangular leukoderma of palmar aspects of the hands. (From Pardo-Castello, *V Arch. Derm.* 1912.)



center and an active raised margin. Coalescence of the lesions is a feature. The distribution becomes more and more symmetric and widespread and the pintids may involve any region although they are found mostly on the exposed areas and over the bony prominences. There are hardly any subjective sensations. In Mexico the early secondary stages were called *empíneas*. They were thought to be a separate entity. Their relation to pinta has only recently been elucidated by León y Blanco<sup>48</sup> (see Pardo-Castello<sup>49</sup>).

The secondary stage gradually passes into the *tertiary* or *dyschromic* stage with the spectacular pigmentary symptoms which have given rise to the name *mal del pinto* (Spanish *pintar* to paint meaning piebald disease). The first dyschromic lesions may appear after one year especially in symmetrical distribution on the hands, forearms, feet and lower legs. However the face, the trunk, and the scrotum may finally be covered with permanent vitiligo-like changes.



Fig. 45.—Pinta. Hyperkeratotic and dyschromic lesions of the palms. (From Pardo-Castello, *V Arch. Dermat.* 1942.)

Especially characteristic is a depigmented area on the volar aspect of the wrist in the shape of a triangle with the base bordering the palm and the apex pointing toward the elbow. Such lesions are composed of irregular sharply outlined spots of hyperpigmentation which in white persons—who are rarely affected—varies from yellow to brown and in colored persons from brown to slate-blue and black, the center being white. Pardo-Castello<sup>49</sup> emphasizes the pepper and salt or mottled arrangement of the pigmented lesions. The discoloration may be found accompanied by follicular and diffuse keratoses and areas of atrophy.

The Wassermann is always positive in this stage. The white patches represent the final stage and do not respond to antisyphilitic treatment which is effective in the other lesions.

The general health seems little affected during this extremely chronic disease which may last several decades. However it is likely that, as in syphilis more internal manifestations will be discovered. Already a high percentage of late cardio-aortic lesions and spinal fluid changes have been reported.<sup>40</sup>

The initial and secondary lesions show essentially the same histological changes, that is, edema of the rete and inflammatory infiltration. The great disturbance of the pigmentary physiology is expressed by the lack of pigment in the basal layer and great accumulations of melanophores in the cutis. Spirochetes are numerous only in active lesions. Late lesions become increasingly atrophic.

The differential diagnosis includes syphilis, yaws, vitiligo, leprosy and certain dyschromic conditions. Seroreaction, the finding of spirochetes and the effect of specific treatment will help. However the differentiation from syphilis and yaws will rest mainly on the clinical appearance. The effectiveness of the same treatment in all these diseases reduces the practical importance of the differential diagnosis.

### Framboesia (Yaws)

Framboesia is a tropical spirochetosis closely related to syphilis although different in many ways. The word frambesia, derived from the French framboise, raspberry refers to the red papillomatous lesions which are a conspicuous feature. The disease is called yaws in English, le pian in French and la boubarole or bouba in the Caribbean area. The causative agent is *Treponema pertenue* a spirochete which is morphologically indistinguishable from *Treponema pallidum*. The infection is endemic among the lower classes of all tropical countries the incidence depending upon the unsanitary conditions rather than on the race. Contrary to a widely held belief that frambesia is predominantly a disease of the colored population it is certain that poor living conditions cause a high percentage of infections among the white population.<sup>41</sup>

Transmission occurs chiefly by direct contact. The fly *Hippelates pallipes*, culex mosquitoes, or leeches possibly play roles as mechanical vectors. Venereal contagion is extremely rare due to the infrequency of superficial mucosal lesions. However penile primary lesions have been observed<sup>42</sup> and are even considered very common in the Cameroons.<sup>43</sup> Congenital infection is questioned by many authors, although claimed by some. Infection with yaws seems to immunize against syphilis.<sup>44</sup>

The incubation period lasts two to three weeks, during which time mild febrile prodromes often occur

<sup>40</sup>Saenz, B. Triana, J. and Armenteros, J. Plata in Cuba. Arch. Dermat. & Syph. 41: 402-418, 1940.

<sup>41</sup>Parde-Castello, V. Framboesia, 800 Cases. Arch. Dermat. & Syph. 49: 782-775, 1930.

<sup>42</sup>Mayr, M. and Neuck, E. G. Framboesia Handb. d. H. u. Gk. 13: 857, 1932.

<sup>43</sup>Haesberger, Framboesia, Arch. f. Schiffs u. Tropen Hyg. 29: Beibl. 2, 1918.

<sup>44</sup>Fox, H. Skin and Tropical Diseases, New England J. Med. 221: 482-483, 1944.

**Dermadromes**—The *primary lesion* called the mother yaw appears usually on the exposed parts of the legs, or much less frequently elsewhere. The initial sore starts as a papule or pustule which soon becomes granulomatous or ulcerative. Such lesions may disappear or become inconspicuous among the great number of almost identical secondary lesions. In a considerable number of cases the primary lesion keeps on growing and develops slowly into an enormous destructive ulcer. Such mother yaw lesions have been seen to remain active as long as twenty years. They may heal with a scar in any stage or may extend peripherally and deeply even to destruction of the underlying bones.<sup>443</sup>



Fig. 55.—Y. Early papulohyperkeratotic plantar lesions (From Pardo-Castello, V. Arch. Dermat. 1939)

Multiple primary lesions and the appearance of satellite papules around the sore are well known.

From six to nine weeks after the infection the *secondary eruption* appears. This is a papular rash often ushered in by prodromal symptoms like fever, muscular pains, and headache. There is a generalized lymphadenopathy (Baermann

after Mayer and Nauck<sup>445</sup>) The secondary exanthem has a peculiar tendency to develop luxuriant papillomatous lesions. These efflorescences may be generalized, grouped about the body orifices numerous or scanty small or large. They may appear as military pin point sized elements as impetigo-like crusty lesions or as raspberry like papillomatous granulomas.<sup>442-448</sup> Most of the secondary lesions disappear but groups of papules arranged in rings (ringworm yaws) or in lichenoid plaques persist during the late secondary period. The soles are often covered with symmetric, deep cornlike painful papules which are surrounded by keratotic eczematoid scaly skin (crab yaws) (Fig. 56) The truly granulomatous and frambesiform nature of such plantar lesions becomes evident after removal of the thick horny top layer.<sup>44</sup> On the palms such lesions may look psoriasiform. Areas of mottled pigmentation and depigmentation on the hands and feet may create a picture which closely resembles pityriasis (Schülfiner's picture in Mayer and Nauck<sup>445</sup>)

The tertiary lesions are seen earlier than in syphilis. A period of late secondary latency is rare. As in syphilis the late lesions may be ulceroserpiginous sometimes of enormous size with a nodular border and a scarred center or deeply destructive and granulomatous. They may destroy joints and bones and cause pathological fractures. Particularly horrifying are the facial and nasopharyngeal mutilations known as *gangosa* which may cause complete loss of the nose and may extend to the lips and lay open the nasal and oral cavities. Later on scarring may cause microstomia and the hands, under similarly destructive and cicatrizing processes may become monstrously deformed and mutilated. Pardo-Castello<sup>449</sup> emphasizes the bone destructive tendency of yaws in contrast to the more osteoplastic nature of the corresponding syphilitic processes.

There is remarkably little involvement of the mucous membranes. Destruction of the soft palate is rare and cardio-aortic and cerebrospinal changes are infrequent.<sup>450</sup>

The pathology of yaws largely follows the pattern of syphilis. The proliferative tendency of the papules, which in syphilis manifests itself in the condylomata is much exaggerated in yaws.

Yaws apparently renders the patient immune, and there seems to be some degree of cross immunity in the later stages of syphilis and yaws.

*Treponema pertenue* is demonstrable in many of the lesions and occasionally in the late gummatous processes which in syphilis is only extremely rarely the case. Wassermann Kahn and the related reactions are positive in 100 per cent of the secondary cases less often in the later stages.<sup>451</sup> The disease is inoculable into monkeys and like syphilis into the anterior chamber of the rabbit's eye and into the testicles of the rabbit.

The treatment is largely the same as for syphilis with the emphasis on the araphenamines and biarsenals. Mercury and iodine are reported to be unsatisfactory. Oral arsenicals for example acetarsone are effective and convenient

<sup>445</sup>Schiffner W. Die Spirochaeta pertenue und das klinische Bild der Frambesia tropica. München und Weisbach p. 1264, 1907.

under primitive conditions.<sup>493</sup> The treatment consists of daily doses of 0.25 Gm for twenty days. These courses are repeated several times after intervals of two weeks. Penicillin has shown promising results.<sup>4</sup>

### Juxta articular Nodes

Subcutaneous movable pea to walnut sized or occasionally much larger nodules of firm or hard consistency occur on the extensor and lateral surfaces of the elbows, knees and other joints.<sup>494</sup> They grow slowly for years usually sym-



Fig. 87—Juxta-articular nodes. Courtesy of Dr. Leon of Dermatology Department of Medicine University of Chicago.

metrically often multiple never in large numbers. The lesions called juxta articular nodes, are tender in the first years of their development but later are painless and stationary. There is no tendency to ulcerate or to heal spontaneously. The affected are as a rule elderly persons.

<sup>493</sup>Whitcomb and Austrian: Two men of Y wu With Penicillin, Bull Johns Hopkins Hosp. 73 233-240 1944

<sup>494</sup>Zakon B. J. and Allen H. Juxta-Articular Nodes, Quart Bull Northwestern Uni Med School 31 270-273 1940

The pathologic picture <sup>300</sup> (Jeanselme after H. Hoffmann <sup>29</sup>) is that of a cyst with a thick, fibrous vascular outer wall in which perivascular inflammatory reactions with foreign body type giant cells and proliferation of blood vessels dominate. Toward the center of the cyst the inflammation subsides, the elastic fibers deteriorate and the nuclei lose their stain. The center is a mass of hyalin or liquid degenerated material.



Fig. 55.—Syphilitic juxta-articular nodes. (From Kala, *7* Arch. Dermat. 1943.)

The nodes are rare in temperate zones and common in the tropics. This is due to the fact that the tropical treponemal diseases especially yaws <sup>301</sup> but also syphilis <sup>302-304</sup> pinta, <sup>305</sup> and bejel <sup>306</sup> are apt to cause juxta-articular nodes in their later stages. Spirochetes were demonstrated regularly in the nodes of thirty-six patients with frambesia <sup>300 305 30</sup>. Patients with active lesions should receive antisyphilitic treatment.

Besides the treponemal diseases several disorders, particularly chronic arthritis may sometimes cause typical juxta-articular nodes <sup>31-36</sup>.

### Relapsing Fever

A group of relapsing fevers is characterized by attacks of severe acute fever lasting two to ten days <sup>37</sup>. The causative organism *Borrelia recurrentis* (*Spirochaeta obermayeri*) discovered in 1868 is a very large spirochete about six times the length of the diameter of a red blood cell and is found in great numbers in the blood during the attacks. It is transmitted by lice bedbugs (Tsetse after Eggebrecht <sup>308</sup>) and ticks <sup>309</sup> probably not by bite but by inoculation from the crushed infected insect body with the scratching nail. There are a number of

<sup>300</sup>Jeanselme J. Über syphilitische Juxta-articuläre Knotenbildungen. Arch. f. Dermat. u. Syph. 1871: 123-127 836

<sup>301</sup>Kala T. and Yen an B. L. Syphilitic Juxta-Articular Nodules Arch. Dermat. & Syph. 43: 826-1-12

<sup>302</sup>Stanton K. H. V. and syphilis Am. J. Trop. Med. 21: 545-552, 1951

<sup>303</sup>Van Dyk and Anderson. Arthritis Histology and Cause of Juxta-Articular Nodes. General Clin. Med. 1943: 41-43

<sup>304</sup>Marink A. and Balachar S. Syphilitic Infection and Syphilitic Juxta-Articular Nodes. Soviet Vet. Med. Dermat. 5: 238-251 254 30 413

<sup>305</sup>Eggebrecht E. Fieber recurrente Vienna 1902 Alfred Hölder

<sup>306</sup>Wischling C. Rückfallfieber in Handbuch der inneren Medizin, Vol. 15 Berlin, 1925 Julius Springer

geographic varieties of relapsing fever differing in vector duration and number of attacks. The relapsing fevers are important in Europe and Africa less so in America where there are some endemic foci in California and Nevada.<sup>147</sup> The first attack starts abruptly after one to seven days of incubation. There may be prostration often vomiting cough splenomegaly and increasing anemia. The attack ends by crisis and the patient recovers remarkably quick but after one to two weeks he has another though often milder attack. Such bouts may recur two three or even five times. The prognosis is good the fatality rate in most epidemics is less than 5 per cent.

**Dermadromes.**—Dermadromes are inconspicuous and inconstant. There is a decided icteric tendency which together with the increasing anemia may create a dirty grayish-brown color. This facial browning was emphasized by the older authors<sup>148</sup> (McCormack after Eggebrecht<sup>149</sup>). With varying frequency in different epidemics, rose spots similar to those in typhoid morbilliform and very rarely scarlatiniform and miliary rashes<sup>150</sup> have been noticed. The relapsing fever roseola is described<sup>151</sup> as appearing at the end of the first attack most frequently on the lateral surfaces of the trunk, on the back on the extensor surfaces of the elbows and about the wrists. Face and legs remain free. The spots are smaller than those in typhoid round purely macular and pink to red in color. They fade after about one hour but since they do not appear simultaneously these spots are visible for a much longer period. The exceedingly ephemeral character of the spots is stressed by other authors.<sup>152</sup> In ten years of experience with American relapsing fever in Nevada Parsons did not notice any rashes (personal communication).

Since the diagnosis rests on the finding of spirochetes in the blood the infrequent exanthems are hardly of diagnostic importance. The usual symptoms accompanying profuse sweats sudamina and mild desquamation are common. *Herpes* was noticed in up to 30 per cent of the cases in certain epidemics. *Petechiae* (which should not be confused with flea bites) and other hemorrhagic symptoms especially nosebleed occur<sup>153</sup> occasionally especially at the end of the attack. It is interesting that the acumen of the older clinicians did not fail to notice that patients with relapsing fever usually show the excoriations pigmentations and pyodermaic infections connected with chronic pediculosis and neglect a state known as *ragabond's skin*.

Specific treatment consists of a few injections of arsphenamine.

### Weil Disease (*Leptospirosis ictero-hemorrhagica*)

Weil's disease (*Leptospirosis ictero-hemorrhagica*) is an acute spirochetal infection with fever gastrointestinal and hepatic symptoms and prostration. After five to six days of high temperature a large percentage of the patients become jaundiced and hemorrhagic tendencies become manifest. The mortality

<sup>147</sup>Morrison, J. K. and Parsons, L. Relapsing Fever. J. A. M. A. 118: 230-22, 1911.

<sup>148</sup>Strong, R. P. Relapsing Fever. Ctr. North America 37: 731-744, 1942.

<sup>149</sup>Oettliger, J. and Halbrech, J. Ephemere Roseola beim Rückfallfieber. München med. Wchnschr. 69: 773-779, 1922.

amounts to about 12 per cent with most of the deaths occurring around the end of the second week.

The causative spirochete is found in the blood

**Dermadromes**—Frequent skin manifestations include icterus and hemorrhagic lesions. Scarletiform, urticarial<sup>40</sup> and other types of rashes are rare.

Non angry endogenous bulbar conjunctivitis and episcleritis are considered early and striking symptoms.<sup>41</sup>

There are milder varieties of *Leptospirosis* for example the so-called inundation or mud fevers in Germany in which morbilliform rashes occur.<sup>42</sup>

### Ratbite Fever (Sodoku)

There exist two clinically similar diseases which develop in man after the bite of rats but which are attributed to different microorganisms. One of these, caused by *Streptobacillus moniliformis* has been discussed under the heading Haverhill fever. Under the name of sodoku which in Japanese means poisoning by a rat the other has been known for centuries only in Japan although it is as cosmopolitan as the rat. Simultaneous infection with both microorganisms occurs.<sup>43-45</sup>

The cause of sodoku *Spirillum minus* (formerly *spirochaeta morsus muris*) was discovered in 1917.<sup>46</sup> It is a fast moving spirochete having only two to five spirals and shorter in length than the diameter of a red blood cell. There are flagella at both ends (B. McDermott after Beeson<sup>46</sup>).

A great number of cases with the spirillum present, have been reported from many countries. In a great number of the cases, children were affected.<sup>47</sup> Epidemics are not known. The disease is rare, one case being recorded among 20 000 hospital admissions in Kansas City. Yet because of its wide use in the treatment of general paresis, the symptomatology of the disease is well known.

*Spirillum minus* is harbored by rats, especially the vicious *Rattus norvegicus* but also in a host of other rodents, and occasionally by cats and dogs. White mice and guinea pigs are susceptible to laboratory inoculation. Animal inoculation with blood taken at the height of a febrile paroxysm is the most reliable method of demonstration.<sup>48</sup> No pure cultures have been grown so far. The organism may occasionally be demonstrated in the serum from a primary lesion in a local lymph node or in the blood<sup>49</sup> with the help of the dark field or with

<sup>40</sup>Larrea, G. J. Studies in Weil Disease I. S. N. M. Bull. 42 280-306, 1914.

<sup>41</sup>Katze, J. Schlämmfieber Kratzenfieber Wasserschlag Felsfieber Infektion durch Leptospiren, Med. Klin. 28 1133-1134 1929.

<sup>42</sup>Rimpau, Felsfieber Mittheilung med. Wchnsch. 85 1977-1979 1932.

<sup>43</sup>Matheis, H. Rattebisskrankung. Ebd. Chir. pp 787-788 1933.

<sup>44</sup>Anderson, V. F. and Spector, D. K. Rat Bite Fever Assoc. ed. W. H. Sporethick, J. Infect. Dis. 84: 314-319 1933.

<sup>45</sup>Futaki, K. Takaki, T. Taniguchi, T. and Otsuki, S. The Cause of Rat-bite Fever J. Exper. Med. 22: 2 9-230 19 6.

<sup>46</sup>Beeson, P. H. Rat-bite Fever Due to *Spirillum minus*, J. A. M. A. 223 322-324, 1942.

<sup>47</sup>Bräking, H. Sodok, Rattenbisskrankheit bei Kindern. Ergebn. d. inn. Med. u. Kinderh. 41 1-45 1932.

<sup>48</sup>Francie, E. Rat-bite Fever and Relapsing Fever in the U. S. A., T. A. Am. Physicians 47 143-151, 1932.

<sup>49</sup>Kortmann, A. G. Two Cases of Rat-bite Fever Surgery 25 623-625 1913.



stains used for spirochetes. Inoculation of mice is more likely to yield results than microscopic procedures, although the accidental occurrence of spirochetes must be ruled out.

The incubation period varies from two to thirty-six days with the greatest frequency between seven and twenty-one days.<sup>221</sup> The outbreak of the disease is often preceded by malaise, headaches, loss of appetite and muscular pains.

**Dermadromes**—The bite wound which is usually healed at the outbreak of the disease changes into a *primary lesion* which may become an indurated and wide ulcer with steep edges, necrotic floor and angry bluish red surroundings.<sup>221-222</sup> In some cases the primary chancre is marked only by a blister (Knowles and Das Gupta after Breinl<sup>223</sup>) or it may be absent. The local lymph nodes are swollen and tender. Later generalized *adenopathy* develops. Acute high fever with chills accompanies the first attack which lasts several days and is almost regularly accompanied<sup>224</sup> by a rash. It should be emphasized that in only 20 to 25 per cent of the cases of *sodoku* which were induced for treatment of general paresis did a rash develop<sup>225</sup> (Teitelbaum after Brown and Nunemaker<sup>226</sup>). This rash may start as a livid erythema around the infected wounds<sup>227</sup> and spread to other parts. Erythema multiforme like papulo-urticarial or macular rashes as well as (Taccone after Brünig<sup>228</sup>) livid *erythematous plaques* up to 14 cm in diameter with or without induration and sometimes with a pale center are common. These lesions are usually not symmetrically distributed<sup>227, 229</sup> (Knowles and Das Gupta after Breinl<sup>230</sup>).

*Petechial pustular and morbilliform exanthems* in sparse or copious dissemination over the entire body only about the joints or in isolated areas have also been observed. A papular eruption in the mouth may occur.<sup>231</sup> A peculiar feature is an acute episode of *urticaria* which occurs shortly before the end of the attack (Wiyake after Brown and Nunemaker<sup>232</sup>). Sometimes severe muscular pains, nausea and vomiting dominate the picture. Edema of the lower legs especially around large indurated plaques<sup>233</sup> is a frequent feature<sup>234</sup> and is considered to be of unfavorable prognostic significance. Leukocytosis is marked. Attacks with flares-ups of the primary lesion as well as of the rash and the other symptoms may recur at intervals of about five days. The number and severity of these relapses vary from six to ten or even more but the bouts generally become milder as immunity develops. The relapsing character of the disease is not always evident since it may consist of prolonged periods of sustained or of daily intermittent fever producing a great variety of clinical pictures. Without specific treatment the disease may pass into a chronic stage.

<sup>221</sup>Breinl C. Die Ratteublenkrankheit. Handb. d. H. 64, 23, 1: 399-41, 1933.

<sup>222</sup>Yam, H. Ra. *ratteublenkrankheit*. Nordst. Utschr. *erkrank* 78: 804-812, 1921. *Id.* 37: 823.

<sup>223</sup>Teitelbaum H. *Leber* O. A. Colby T. Koenig J. T. Schmidt O. H. and Saunders A. 21.

<sup>224</sup>Wiyake T. *Parasit* 34: 31 A, 93: 772-773, 1939.

<sup>225</sup>Teitelbaum H. *Leber* O. A. Colby T. Koenig J. T. Schmidt O. H. and Saunders A. 21.

<sup>226</sup>Wiyake T. *Parasit* 34: 31 A, 93: 772-773, 1939.

<sup>227</sup>Knowles

<sup>228</sup>Knowles I. *Ein Fall* von Ra. *ratteublenkrankheit*. *Nordst. Utschr. erkrank* 99: 261-264, 1917. *Id.*

<sup>229</sup>Id.

<sup>230</sup>Wiyake T. *Parasit* 34: 31 A, 93: 772-773, 1939.

In some cases, severe sensory or motor nervous symptoms prevail. Diffuse and patchy alopecia has occurred in later stages. The hair grew back after general improvement.<sup>86</sup>

The Wassermann reaction and related tests become positive in 50 to 60 per cent of the cases.<sup>86</sup>

The mortality of the treated patients is low. No fatality occurred among 125 cases reported in the United States.

The clinical diagnosis must take into account a great many fevers, although the history of a ratbite, the primary lesion and the laboratory findings will secure the diagnosis. The differentiation from rat bite transmitted Haverhill fever is made by the laboratory findings<sup>86</sup> as well as by the presence of arthritis and the lack of a pronounced primary chancre in Haverhill fever. Haverhill fever after ratbite is probably more common than nodoku.

Specific treatment consists of from three to ten injections of neoarsphenamine or similar arsenicals. Bismuth is also effective.<sup>87</sup> The first administration of specific drugs may be followed by a Herxheimer reaction.<sup>88</sup> Recurrences have been seen after less than three injections.

The therapeutic inoculation of the disease into patients with general paresis instead of malaria was done in a great number of patients, but has been abandoned because complications occurred and control of the infection often proved difficult.

### African Trypanosomiasis

The trypanosomiasis of central Africa (sleeping sickness)<sup>89,90,91</sup> is caused by the flagellates *Trypanosoma gambiense* and *Trypanosoma rhodesiense*. These microorganisms are blood parasites of many wild and domesticated large mammals for example oxen, sheep, and antelopes, and are transmitted to man by the bite of the tsetse fly *Glossina palpalis*. The transmission is cyclical and mechanical. The trypanosomes are most abundant in the blood during the febrile attacks, but they are also found in the lymph nodes, the cerebrospinal fluid and serous fluids. They can be stained, demonstrated by dark field and cultivated on salt agar (NNN medium).

The disease is endemic and at times epidemic, in large parts of equatorial Africa especially around lakes and along rivers where the tsetse fly lives. At times the population of large areas is decimated by the disease which affects the colored races as well as the white. The infecting bite is often immediately or within a week,<sup>92</sup> followed by local inflammation. These primary chancres do not develop invariably but furunculoid and ulcerative lesions, with regional

<sup>86</sup>Casati, A. Rat-bite Fever Proc Roy Soc Med 27: 1578, 1934

<sup>87</sup>Ozeki, Y. As subkutanerkrankheit leistungsmethod des Kroggers, J. p. J. Dermat. & Urol. 22: 46 1922 24 42 84

<sup>88</sup>Macdonald, P. H. Manual Tropical Diseases, London, 239 Cassell & Co Ltd.

<sup>89</sup>Kocherberger, E. R. African Sleeping Sickness, M Clin North America 27 833-847 1942.

<sup>90</sup>Jayer, M. Hanterschleimern bei exotischen Krankheiten Trypanosomiasis, Handb d.

II Gl. 12, 1 190-193, 1922

<sup>91</sup>Graf, H. Beitrag zur Pathologie des Glossina palpalis-Stichs und der Inkubationszeit bei Schlafkrankheit, Arch f Schiffs- Tropen-Hyg 22: 219-222 1929

lymphatic involvement fever and the local presence of the trypanosomes have been observed beyond doubt.<sup>209-211-212-213</sup> About two to three weeks after the infection the patient is stricken with fever of varying intensity and course the



Fig. 50—African trypanosomiasis. Secondary eruptions. (From L. Omer, courtesy The Annals of Tropical Medicine and Parasitology The University Press of Liverpool.)

irregularity being a diagnostic feature.<sup>214</sup> The patient becomes weak and anemic and his mental abilities suffer. General lymphadenopathy is a constant though varying feature with the lymphatic nodes at first being soft later hard. Head

<sup>209</sup>Géry L. R. Les phénomènes cutanés au cours de la trypanosomiose à malice en partie dans la race blanche. Thèse de Paris 1910.

aches, paresthesias, and a peculiar kind of deep hyperesthesia on knocking against a hard object known as Herandels sign indicate the early nervous involvement.

**Dermadromes.**—The primary lesion has a deep red center surrounded by a pearly white venular zone and a red halo.<sup>423</sup> Erythema and infiltration around the bite may persist far into the secondary stage. The bite however differs in its appearance from the more transitory *secondary eruptions*<sup>424,425</sup> Characteristic of the early secondary stage but not present in all patients nor at all times,<sup>426</sup> are *urticarial erythemas* in large round patches, rings, or crescents which have a decided tendency to spread peripherally and heal in the center. Coalescing circinate rather large patterns may cover the entire back.<sup>427,428</sup> These trypanids are of unpredictable and fugitive nature. They may be without change for days or even several weeks and then they may evanesce quickly reappearing in other places. The erythemas are slightly raised but not or little infiltrated<sup>429,430</sup> pink in color of normal temperature often sensitive and sometimes very itchy, especially if they are of a more exudative papular type.<sup>431</sup> Erythema nodosum occurs.<sup>429,432</sup> The blood taken from lesions contains more trypanosomes than the peripheral blood of the other skin. The relatively delicate erythema is difficult to detect in colored skin. In some cases the erythema is annular and linear<sup>433</sup> like the erythema annulare encountered in rheumatic fever.

Localized edema especially of the face is common in the secondary stage.<sup>434,435</sup> Another dermadrome is a vascular bluish mottling independent of the erythemas (Master after Mayer<sup>436</sup>)

The fading skin lesions do not leave any trace.<sup>437</sup> The secondary stage may last a long time seven years usually being considered the maximum. The skin manifestations become less marked and less frequent and gradually the disease drifts into the sleeping sickness stage with deep mental changes, stupor and somnolence during daytime restlessness at night muscular twitchings tremor and convulsions. Hepato-splenomegaly is present. If not treated death is profound cachexia is inevitable.

During the *encephalitic* stage early features, including erythema may still be present. The gross pathology is meager. Microscopically perivascular round cell infiltrations can be seen throughout the brain and especially in the erythematous skin.<sup>438</sup>

The *diagnosis* rests on the finding of trypanosomes in the blood in the lymph node material or in the spinal fluid. The clinical diagnosis of trypanosomiasis

Dr. Kellersberger of the American Mission to Lepers, who has had an almost unique experience with African trypanosomiasis does not believe that the rashes are very commonly seen, since most of the patients in the reservec centers he examined had advanced cases and the colored skin makes the erythemas difficult to observe personally (communication).

<sup>423</sup>Stage II. Sleeping Sickness, Med. Week. 13 1422-1423, 1929.

<sup>424</sup>Chavallier P and Lévy G. Les éruptions précoces de la maladie de sommeil. Bull. Soc. franç. de dermat. et syph. 23 185 1928.

<sup>425</sup>Darré H. Les Symptômes cutanés de la trypanosomiose humaine. Ann. de dermat. et syph. 6 672, 1904.

<sup>426</sup>Owens, D. C. Clinical Notes. Trypanosomiasis, Ann. Trop. Med. 22: 47-52, 1928.

<sup>427</sup>Andry G. Erythème annulaire centrifuge et trypanosomiose, Bull. Soc. franç. de dermat. et syph. 29: 124-126, 1923.

may be extremely difficult especially in persons who have moved from Africa to other countries. The large erythematous-urticarial centrifugal and annular erythemas are a most valuable sign. Together with internal manifestations they are almost diagnostic. Arsenic as trypanamide pentamidine (M & B 800) and naphuride (Baeyer 205 germanin) are considered of high value.

### American Trypanosomiasis (Chagas Disease)

American trypanosomiasis is caused by *Trypanosoma cruzi* and transmitted from infected persons and reservoir animals (armadillo opossum) by various species of *Parstrongylus tritoma infestans* and other bugs.



Fig. 60—Chagas disease. Primary lesion (inoculation chagoma, fourth day) (Courtesy Misión de Estudios de Patología Regional Argentina, Jujuy Argentina.)

Skin Manifestation have long been considered of little importance. Recently however NAXXA and his associates<sup>43-45</sup> demonstrated their significance

<sup>43</sup>NAXXA, S. and Freije, R. Manifestaciones cutáneas d inoculación (Chagomas) y hematomas en enfermedad de Chagas. I. Universidad Buenos Ayres, Misión de Estudios de Patología Regional Argentina Jujuy) Publicacion 66 pp 3-57 1960.

<sup>44</sup>NAXXA, S. and Freije, R. Chagoma de inoculación, seguido de equinostripanide morbiliforme. Ibid Publ 46, pp 55-61 1960.

<sup>45</sup>NAXXA, S. and Nijara, M. Chagoma d inoculación y equinostripanide pellucida. Histopatología, Ibid Publ 46, pp 63-101 1960.

<sup>46</sup>NAXXA, S. Basco, G. Basco, R. and Com, D. Chagoma antibrachial chag múltiples metastásicos hematógenos y complejo oftalmogangliones. Ibid Publ 46, pp 105-11 1960.

<sup>47</sup>NAXXA, S. and Basco, G. Chagoma hematogénos, Ibid Publ 45 1960.

<sup>48</sup>NAXXA, S. and Jörg, M. E. Chagoma experimentales, Ibid Publ 47 1960.

<sup>49</sup>NAXXA, S. and others. I. reacciones enfermedad de Chagas. Ibid Publ 45 1960.

<sup>50</sup>NAXXA, S. Equinostripanide alveolares tardías en enfermedad de Chagas y otras manifestaciones eruptivas, Ibid Publ 71.

<sup>51</sup>NAXXA, S. and Aranda, C. A. Fused crabs bei der amerikanischen Leishmaniasis Arch f chile- Tropen-Hyg 35 553-561 1971.

in a series of important investigations. A primary skin lesion may appear as a large dark red prominent and deeply infiltrated nodule with or without intact epidermis (Inoculation Chagoma) which is histologically characterized by fat necrosis. Lymphangitis follows the primary lesion. The inoculation often occurs on the face especially about the eye. Thus, the first symptom often is a bipalpebral unilateral edema with conjunctival injection. This eyelid edema lasts about four weeks (Romaña's sign).



Fig. 61.—Chagas disease. Unilateral and bipalpebral edema and conjunctivitis. (Romaña's sign). About three weeks after infection. (Courtesy Misión de Estudios de Patología Regional Argentina, Jujuy, Argentina.)



Fig. 62.—Chagas disease. Eight five days old. (Courtesy Misión de Estudios de Patología Regional Argentina, Jujuy, Argentina.)

As early as five days after the infecting bite a papular rash in the neighborhood of the bite a generalized circinate morbilliform or scarlatiniform erythema and cutaneous and subcutaneous nodules some of large size have been observed. These nodules are very firm and deep red if they arise from the more superficial strata. Maxza also describes impetiginous and ulcerative eruptions seen several months after the infection.



Fig. 63.—Chagas disease. Rash 8 days old. (Courtesy Mission de Estudios de Patología Regional Argentina, Jujuy, Argentina.)

Since the thyroid is often affected in the later stages dermadromes which occur in myxedema may be encountered. Edema of the face and skin and also *bronzing* are mentioned. The South American authors consider treatment with Bayer 7602 of great value but the drug the formula of which is secret still lacks general recommendation because of the danger of nephritis.<sup>44</sup>

A skin test with a cruzin has been developed. The diagnosis however rests mainly on the microscopic and cultural evidence of trypanosomes in the patient's blood.

<sup>44</sup>Mayer and Pfano. Abstracted i Trop Dis Bull 20: 290 1942.

<sup>45</sup>Mackie Th. T. Hanter E. W. and Brooks Worth C. A Manual of Tropical Medicine Philadelphia, 1945 W. B. Saunders Company.

### Leishmaniasis

The leishmanias are flagellated protozoans which are capable of producing a group of diseases which are all of dermatological interest. Two of them oriental sore and American leishmaniasis (espundia) and possibly a third disease tropical granuloma inguinale are predominantly skin diseases and therefore will not be discussed. Visceral leishmaniasis or Kala-azar however is an internal disease with specific skin manifestations. It occurs in an infantile and in an adult form which are closely related.

The causative protozoan is a small ovoid or round body found either free or in cells of the reticulo-endothelial system particularly in the spleen the liver and the bone marrow. In cultures on blood or salt agar (NNN medium) they assume the characteristics of flagellates and are inoculable into dogs and monkeys. The disease is endemic in the Mediterranean and the Near and Middle East especially in India which has been visited by great epidemics. Sandflies (*Phlebotomus*) are now considered as vectors with dogs as a reservoir particularly in the Mediterranean area.



FIG. 51.—Post-kala-azar dermal leishmaniasis in an incompletely treated case of visceral kala-azar. Depigmented nodules over the nose. (Courtesy Dr. A. K. Ghosh Dastidar.)

The incubation period is over ten days; long latency may occur. Mirsoian<sup>40</sup> claims to have found the primary lesion in inconspicuous lentil-sized papules on the faces of children who several months later showed secondary symptoms of infantile kala-azar. The lesions which contain leishmanias, may still be present at the time of the outbreak of systemic symptoms or they may have healed and left pigmented spots. The onset is insidious or abrupt with spiking fever which

<sup>40</sup>Mirsoian, N. A. Primary Lesions of Visceral Leishmaniasis in Children. *Trop. Dis. Bull.* 66: 294-298, 1943.



may last many weeks. Then an afebrile period with improvement may occur followed by a relapse of fever. After several attacks a chronic state of emaciation, low temperature and anemia becomes established. Gradually the liver and spleen enlarge to tremendous size—the big protruding abdomen contrasting sadly with the thin limbs. The appetite remains good for a remarkably long time. Unusually low leukopenia and later ascites and edema are common. Death is caused by cachexia or intercurrent disease for example dysentery or noma. The microscopic pathology shows abundant leishmanias in the reticulo-endothelial system.

**Dermadromes.**—The skin gradually takes on a claylike gray or dusky color especially on the hands and feet. This mixture of pallor and pigmentation is seen in white as well as in colored races.<sup>41</sup> The dusky color accounts for the



FIG 65



FIG 66

Fig 65—Port-kala-azar dermal leishmaniasis. Person of dark complexion. Small nodules on the partly depigmented skin area on the chin, from one of which *Leishmania donovani* could be demonstrated in the smear. Sharply defined depigmented spots are seen over the chest, shoulders and face. The last had visceral kala-azar one year ago and, as treated with 7 Gm of arsenobismar, which is much less than the therapeutic dose. (Courtesy Dr R. K. Ghosh Dasgupta.)

Fig 66—Noma as complication of kala-azar. Stereal puncture smear showed *Leishmania donovani*. (Courtesy Dr R. K. Ghosh Dasgupta.)

name kala-azar meaning black fever. Petechiae and other hemorrhagic lesions, especially bleeding gums are common. With the progressing cachexia small ulcerations about the elbows and knees and occasionally larger ulcerations along the legs may develop. Specific papules and gangrenous ulcers containing leish

mania occur<sup>244</sup> as well as secondary cachectic ulcerations, such as noma. A most interesting cutaneous form of kala-azar<sup>245,246,247</sup> has become known as the *post kala-azar leishmanid*. Eighty per cent of the patients were known to have had kala-azar and to have been treated with antimony. Of the rest (Napier after Mayer<sup>247</sup>) a previous kala-azar infection could be assumed. The eruption starts with erythematous or depigmented patches on the face especially about the nose and mouth. Such macules, resembling leprosy may later appear on the limbs and on the trunk (see colored illustrations in M. Mayer<sup>247</sup>) but the chin, the upper lip and the eyebrow region are most frequently and most heavily involved. The macules are often followed by nodules which however may also appear first. These nodules are pea-sized or a little larger semiglobular firm nonulcerating and covered with atrophic skin. Their color at first is red later becoming decidedly orange. They may coalesce and form ridges of tuberculous lesions, which resemble xanthoma tuberosum multiplex. The nodules contain only few leishmanias mostly in giant cells in the center of a granuloma consisting mainly of macrophages and fibroblasts. The hypothesis has been advanced that some, possibly antimony fast leishmanias remain in the skin and cause the local recurrences.

The diagnosis of kala-azar may be suggested by the geographical location and the resistance of the fever to quinine. The finding of leishmanias by splenic or sternal puncture is diagnostic.

Kala-azar is treated with antimony compounds. The post kala-azar leishmanid does not respond well to this drug. It may become arrested in the late xanthomatoid form and remain without changing.

## Malaria

There is no cutaneous lesion invariably or even frequently connected with malaria. Physicians of malaria free countries are inclined to visualize the malaria patient as having a sallow skin. This is only occasionally true. In countries where malaria occurs usually a high percentage of the population is infected and suffers from attacks. However the typical *malarial color* a dirty yellowish brown sallow hue which in relatively rare instances may gradually take on deeper shades with a greenish component is rare. The yellowish discoloration is more pronounced immediately after an attack and may approach a bronze shade as in blackwater fever.

*Diffuse discoloration* of the skin in malaria may be due to anemia from the destruction of the erythrocytes to icterus, or to hyperpigmentation. Occasionally melanemia caused by large amounts of free malaria pigment in the blood serum may influence the skin color. The hyperpigmentation may compare with

<sup>244</sup>Shapiro, Y. M. and Dineh, S. Kala-Azar in Palestine Case With Cutaneous Lesions, Tr. Roy Soc Trop Med. & Hyg 33 257-262 1939

<sup>245</sup>Arten, H. W. and Napier, L. E. Post-Kala-Azar Dermal Leishmaniasis Indian J. M. Research 15 97-106 1937

<sup>246</sup>Brakhauchari, U. N. A New Form of Cutaneous Leishmaniasis—Dermal Leishmanoid, Indian M. Gaz 57 124-127 1932

<sup>247</sup>Napier and collaborators. Post Kala-Azar Dermal Leishmaniasis. A Series of Publications, Indian M. Gaz, 1939 and 1940

addisonism in intensity and distribution including oral manifestations. Racial pigmentation of the gums can be ruled out by the effect of specific treatment which however removes malarial pigment deposits but slowly. Many authors have suggested that the adrenal cortex plays a part in the formation of the cutaneous pigment in malaria and there is some pathological evidence to support the clinical facts. F. Rosenthal and Löwenthal<sup>44</sup> found in such a case almost complete atrophy of the adrenals. Two types of pigment occur in the skin. The



FIG. 67. Malaria tropica chlorosis facialis and the early-shaped pigmentation of the cheeks. Malarial pigment has been described in bilharziosis, ankylostomiasis and other conditions. (Courtesy Prof. A. Marchionni, Ankara, Turkey.)

specific malarial pigment (hemozoin) is derived from the destroyed red cells. It contains iron but because of its firm grasp on the iron atom does not give the ordinary Berlin blue (Potassium ferrocyanide and  $\text{FeCl}_3$ ) reaction. It is taken up by the reticulo-endothelial system discoloring mainly the spleen, liver and bone marrow and in extreme cases it may be found in the lumen of capillaries. The skin does not store the pigment however it may be found in blood vessels.

<sup>44</sup>F. Rosenthal, F. and Löwenthal, A. Addison infolge Malaria Zentralbl. f. B. 111 (Gruiblerstr. III 1931 1932).

Hemosiderin occurs besides the malaria pigment. Skin pigmentations in malaria may also be caused by *melanin*<sup>86</sup>. Chloasma like spots on the face are not rare. These sometimes occur<sup>86</sup> as the peculiar mustache-shaped variety called chloasma periorale<sup>87</sup> which like many dermatoses of the lips leaves a thin white border



Fig. 64—Malaria tropica morbilliform rash (Courtesy Prof. A. Marchionini, Ankara, Turkey)



Fig. 65—Cyanosis in malaria tropica (Courtesy Prof. A. Marchionini, Ankara, Turkey)

line between it and the vermilion area. Sometimes the pigmentations in malaria are pell-grond in distribution being found over the dorsa of the hands and the knuckles.

<sup>86</sup>Kaufmann K. Die pathologischen Pigmentierungen der Haut. In: Innere Medizin, Neurologie und Psychiatrie. Handb. d. Klin. Ch. 4, 2. 1011-1221. 1932.

<sup>87</sup>Arborelius A. Malaria. Malarious Chloasma. Clinical study. Acta dermat. venerol. 21: 299-319. 1940.

<sup>88</sup>Pole P. V. Durch Funktionsstörungen des weiblichen Genitalsystems hervorgerufene Hautkrankungen. Derm. Wchnschr. 83: 282, 1906.

addisonism in intensity and distribution including oral manifestations. Racial pigmentation of the gums can be ruled out by the effect of specific treatment which however removes malarial pigment deposits but slowly. Many authors have suggested that the adrenal cortex plays a part in the formation of the cutaneous pigment in malaria and there is some pathological evidence to support the clinical facts. F. Rosenthal and Löwenthal<sup>64</sup> found in such a case almost complete atrophy of the adrenals. Two types of pigment occur in the skin. The



Fig. 67—Malaria *repta chlorasma periorale* and butterfly-shaped pigment (brown) on the cheek. Malarial pigment ions have been described in bilharziosis, schistosomiasis and other conditions. (Courtesy Prof. A. Mavridis, Ankara, Turkey.)

specific *malarial pigment* (hemazoin) is derived from the destroyed red cells. It contains iron but because of its firm grasp on the iron atom does not give the ordinary Berlin blue (Potassium ferrocyanide and HCl) reaction. It is taken up by the reticulo-endothelial system, discoloring mainly the spleen, liver and bone marrow and in extreme cases it may be found in the lumen of capillaries. The skin does not store the pigment, however it may be found in blood vessels.

<sup>64</sup>Rosenthal F. and Löwenthal H. Addison infolge Malaria. *Zentralbl. f. Bakt.-u. Grenzgeb.* 21: 231, 1921.

relapses of chronic malaria in up to 30 per cent of their cases. In malaria countries it seems good advice to look for the parasites in cases of chronic and unexplained urticaria or even to try quinine as a diagnostic test.

Petechiae, purpura, and other *hemorrhagic* symptoms have often been reported. In some of these cases<sup>100</sup> it could be shown that the petechiae were caused by arterial or capillary *thrombi* and vascular wall infiltration. *Plasmodia* could be demonstrated in the lesions. Circulatory disturbances of the hands and feet may cause painful sensations of heat, as well as other paresthesias.

*Gangrene* of circumscribed areas, with or without Raynaud like symptoms and sometimes necessitating amputation is on record in a considerable number of cases.<sup>101-104,106</sup> It is probably caused by endarteritis. In the course of chronic malaria occasional dermatomes may occur due to the severe anemia (for example *coilonychia*<sup>105</sup>). The resistance to secondary infections is decidedly lowered. Leishmaniasis cutaneous diphtheria, and other secondary infections may take an unusual course. The most spectacular secondary infection is *noma*. A Eckstein<sup>106</sup> (in Turkey) found malaria in nineteen out of twenty two cases. The patients were mostly small boys. There is a striking parallel between the incidence of *noma* and the malaria mortality in seasonal as well as in regional respects.<sup>107</sup>

### Noma (Cancerum Oris; Stomatitis Gangrenosa)

Noma is a rare disease in western civilization. Eckstein<sup>106</sup> saw only one case in ten years of service at the Düsseldorf Children's Clinic, while he observed no less than forty cases during three years in the Children's Hospital at Ankara, Turkey. Similar experiences have been reported from China. Epidemics of *noma* were observed in former years in European hospitals. Almost exclusively a disease of childhood *noma* is predominantly a nonspecific complication of acute infectious diseases. Measles, typhoid,<sup>108</sup> congenital syphilis<sup>109</sup> and particularly malaria<sup>110</sup> are known to create the conditions in which the peculiar gangrene of the cheek occurs. Agranulocytosis and acute leukemia are other predisposing diseases.<sup>111-113</sup> Some cases without known preceding disease have occurred.

The clinical picture shows a gangrenous stomatitis, which sometimes in a fulminating manner breaks through the cheek and upper lip and destroys all tissues, including the bone and teeth which lie in its path. Then the well known horrible destruction of one cheek surrounding the nose results. The lesion is

<sup>100</sup>Fraser L. and Fraenkel E. Das Malariaexanthem im klinischen und pathologisch-anatom. Abde. Arch. f. Schiffs- Tropen-Hyg. 25: 333-363 1921.

<sup>101</sup>Dave H. E. Cutaneous Affections in Various Diseases Brit. J. Dermat. 28: 41 1906.

<sup>102</sup>Lee K. Gangrene of Feet in Acute Lari. Pernicious Malaria. Arch. ed. et id. Soc. Ital. di chir. 61: 1015-1021 93.

<sup>103</sup>Eckstein A. Stomatitis Gangrenosa. Am. J. Dis. Child. 29: 319-327 940.

<sup>104</sup>Labar S. J. and Ross D. E. A Case of Cancerum Oris Following Typhoid Fever With Pusill. Republ. Canad. M. A. J. 33: 4 6-440 931.

<sup>105</sup>Palmer W. Noma. Basel, 1927. Dissertation.

<sup>106</sup>Eckstein A. Zur Krankheitsaufassung der Noma und gleichartiger Formen des Gewebestodes. Zentralbl. f. Chir. 85: 225-1863 875.

<sup>107</sup>Eckstein A. Infectious Gangrene of the Skin Due to Bacterial invasion. Arch. Surg. 21: 223, 1923.

decidedly unilateral causes little or no pain and temperature and even appetite are much closer to normal than one would expect a surprising observation which can also be made in the final stages of destructive oral cancers.

There is no strong leukocytic reaction<sup>66</sup>. Only in the late stages does general totemia develop. The post mortem examination reveals necrotic and degenerative liver and spleen changes. The mortality as based on 175 cases from the literature is 95 per cent. Eckstein<sup>66</sup> after switching from neoarsphenamine which proved disappointing to antiganrene serum in large doses locally intramuscularly and intravenously had more than 50 per cent recoveries in twenty one cases.

Although there is no complete agreement about the cause it is assumed by most authors that Plaut Vincent's symbiosis of fusiform bacilli and spirillae plays an important part. These microorganisms have frequently though not always<sup>67</sup> been found in the lesion and in the surrounding apparently normal tissues<sup>68</sup>.

### *Amebiasis Cutis*

Ulcerations of the skin caused by *Endamoeba histolytica* occur in amebiasis either in connection with an operative abdominal wound or around the anus or without direct connection with the infected viscera for example on the glans penis. The amebic ulcers<sup>69</sup> are rapidly spreading lesions. Varying activity in different portions of the margin causes an irregular jagged outline. The edge is undermined purulent and surrounded by a red halo. The floor is covered with indolent granulations and pus. The skin lesions respond to emetine.

<sup>66</sup>Friedlander J. Über Vomer der Wangen Schleim und Wucher 1920 I 251 255

<sup>67</sup>Engelman M F J and McHenry H E. Amebiasis Cutis (*Endamoeba histolytica*) Arch Dermat. & Syph 25 1 23 1931

## CHAPTER VII

### SYSTEMIC INFECTIONS

#### Rickettsial Diseases

Rickettsial diseases of man and many animals are caused by gram-negative coccoid or bacillary intracellular microorganisms which are usually borne by arthropods especially lice and ticks and which need tissue-containing media for successful culture. With the exception of the rickettsiae of the otherwise different Q fever they are not filtrable.<sup>775</sup> The serum of patients with rickettsial diseases agglutinates specifically certain strains of *Bacillus proteus* (Weil-Felix reaction). The clinical appearance of the rickettsioses of the typhus group is best illustrated by its most important representative typhus itself from which the others differ but little.

#### TYPHUS FEVER

Typhus fever (typhus exanthematicus) is a severe endemic and epidemic disease the importance of which for the human race equals that of plague and cholera.<sup>774</sup> It has accompanied most of the wars and famines and other upheavals of history. Its victims in Ireland during the early decades of the nineteenth century numbered millions. The epidemic form is possibly with a few exceptions spread by body lice. After an incubation period of thirteen to fourteen days, the patient suddenly develops fever, chills, severe headaches and prostration. The fever is continuous, ending by rapid lysis after approximately two weeks. Temporary mental disturbances during the fever and insomnia are common. The attack is followed by a long period of convalescence which may last two or three months. The attack is characterized by a rash, stupor, low blood pressure, tender and enlarged spleen (denied by Gordon<sup>775</sup>) and various gastrointestinal and renal symptoms. The loss of weight is very marked.<sup>78</sup> The blood shows a shift to the left and thrombocytopenia which may reach 100,000 during the fifth to eleventh days.<sup>79</sup> The mortality rates vary widely. Children and groups who have been exposed for a long time to infestation with lice are often only mildly ill. In people beyond 50 years of age, in the undernourished and in newcomers from disease-free countries who are not accustomed to body lice, for example physicians and nurses, the disease is apt to take a more severe course with mortality rates higher than 50 per cent.

<sup>775</sup>Dyer, R. E. The Rickettsial Diseases, J. A. M. A. 126: 3165, 1944.

<sup>776</sup>Kilmer, H. Body Lice and History, New York, 1938, Little Brown & Company.

<sup>777</sup>Gordon, D. M. Rickettsial Disease, J. Michigan M. Soc. 88: 653-658, 1940.

<sup>778</sup>Thoms and Rickettsial Diseases, Harvard University Press, Cambridge, Mass., 1910, article by J. E. Gordon, pp. 624-671.

<sup>779</sup>Wickström, A. Das Fleckfieber Handb. d. inn. Medizin 8: 643-676, 1923.



The gross pathology is unrevealing but the severity of the systemic infection is shown by typical widespread microscopic vascular lesions in the central nervous system the heart and especially the skin



Fig 72 Typhus lesion on the second day of exanthem. Stilling of the endothelial cells and well defined perivascular cellular reaction. (Courtesy Wood, J. D., Th. H. and Blaser, F. P. J. A. M. A.)

The infection conveys a lasting immunity.

The diagnosis is based on the clinical picture, the epidemiologic conditions and the Weil-Felix reaction. Sometimes complement fixation tests and biopsy of a skin lesion are useful.

**Dermadromes.**—The importance of the rash is reflected in the various names of the disease such as spotted fever, typhus exanthematicus, Fleckfieber, fièvre exanthématique. Murchison (after Curschmann<sup>46</sup>) collected nineteen different terms referring to the rash.

In the first two days of the fever an *initial exanthem* consisting of a few 3/4 mm wide petechial papules on the trunk can sometimes be observed.<sup>47</sup> The initial exanthem may occasionally be morbilliform or urticarial.<sup>477</sup>

<sup>46</sup>Curschmann H. Das Fleckfieber. Nothnagel, Spezielle Pathologie und Therapie Vol. III. Wien, 1900. Alfred Hölder.

<sup>47</sup>Lipschitz B. Die Klinik des Fleckfieberexantheus. Arch f. Dermat. Syph 128: 414-437. 1919.

The main rash appears most often on the fourth to sixth day of the fever rarely as early as the second or as late as the ninth day.<sup>340</sup> The eruption is often preceded by a characteristic drop in temperature. In the early stages before it becomes plainly visible the rash can be demonstrated by a warm bath or a tourniquet.<sup>341</sup> The most comprehensive dermatological evaluation of the rash has been given by Lipschutz.<sup>379</sup> This article contains excellent illustrations.

The rash appears continuously and not in a series of crops so that the definite number of spots is reached within one or two days.<sup>378</sup> The eruption begins on the upper abdomen and chest then in rapid succession spreads to the back and to the extremities. The armpits and the inner surfaces of the upper arms are the places to look first for spots.<sup>380</sup> The fully developed rash may be extremely copious with the greatest density on the trunk. From the trunk to the arms and to the face the density decreases on the whole with some accentuation on the dorsa pedum which is in contrast to the scarcity of lesions on the thighs and lower legs. Eruption on the palms and soles is not the rule. The exanthem starts with pale, ill-defined pinhead to lentil-sized hardly palpable often irregular maculae which as soon as they have reached a few millimeters in size no longer fade completely under glass pressure. Confluence of neighboring lesions into irregular and slightly raised spots occurs. The color is not bright red but has an increasingly brownish tinge. This indicates the *hemorrhagic component* which manifests itself in more or less numerous petechiae within and between the spots. The purpuric phenomena are a measure of the severity of the infection.<sup>377</sup> Purpuric lesions are often found in the folds and on the back. In the mature stage which is reached around the twelfth day the color is decidedly purplish and a delicately bluish marbled vascular pattern may be seen between the lesions which is easier to recognize from a short distance in moderately bright light. The old physicians called this subcuticular mottling or mulberry rash (Buchanan and W. Jenner after Bäumer and Aschoff<sup>382</sup>). After the twelfth day the exanthem fades leaving yellowish brown pigmentation which may persist for a while. A slight branny desquamation which can be provoked by gentle rubbing takes place during and some days after the fading.<sup>381</sup>

In up to 20 per cent of the cases trying with the epidemics no exanthem could be observed. A macular erythema is occasionally seen on the buccal mucosa. It precedes the exanthem. Initial conjunctivitis is common. Herpes is rare. The nails often register the severe disease by a white transverse line (Botkin and Pietnew after Schlittenhelm<sup>377</sup>). Pietnew<sup>383</sup> saw longitudinal futed lines.

The *micropathology* of the lesions has been studied by E. Fraenkel<sup>384</sup> and Bäumer and Aschoff.<sup>377</sup> There are foci of hyaline degeneration necrosis and

<sup>377</sup>Botkin H. Fleck typhus. *Moskauer Epidemic 1917-1920*, Ztschr. f. klin. Med. 82: 253-301 1922.

<sup>378</sup>Frank. Klinische und ophthalmische Beobachtungen bei Flecktyphus. *Veröff. d. a. d. Oph. d. Med. d. Kaiserl. 14* 111 124 1923.

<sup>379</sup>Oyer R. E. Typhus. I. *The North America 27* 774-786 1942.

<sup>380</sup>Bäumer (and Aschoff) L. *Flecktyphus Med. Wirtsch 21* 783-799 1918.

<sup>381</sup>Deleau. Not sur la desquamation postérieure dans le typhus exanthématique. *Bull. Acad. de med. 86* 304-307 32.

<sup>382</sup>Fraenkel E. Zur pathologischen Anatomie des Flecktyphus. *München. med. Wochenschr 69* 969-971 1921.

endothelial proliferation in the intima of the small arteries and precapillaries. These lesions form protruding intravascular buds and may give rise to small thrombi. In the endothelial cells rickettsias have been found in small numbers.<sup>446</sup> Furthermore there is a perivascular infiltration of lymphocytes plasma cells and epithelioid cells which resemble adventitial histiocytes. These changes are found in the papillary vessels of the skin and especially throughout the brain and heart.

No specific treatment is known. A prophylactic vaccine is available.

A mild variety of typhus known as Brill's<sup>447</sup> disease endemic or murine typhus with a mortality rate of less than 4 per cent is endemic in the east and southeast of the United States and in many ocean harbors. The disease is harbored by rats and transmitted by rat fleas and rat lice.<sup>448</sup> The exanthem was seen in 64 per cent of 115 cases<sup>449</sup> appearing about the fifth day starting on the trunk and spreading centrifugally rarely reaching the face and palms. There often were only a few maculopapular lesions of 2 to 5 mm in diameter.

### ROCKY MOUNTAIN SPOTTED FEVER

Much more dangerous than endemic typhus is Rocky Mountain spotted fever. Approximately 600 cases occur every year in the west and 200 additional cases in the remainder of the United States. The average mortality is 12 1/2 per cent. This rickettsiosis is caused by *Rickettsia rickettsii* and transmitted by various ticks.<sup>450</sup> The clinical picture resembles typhus closely. A mottled initial rash has often been seen to appear with the fever thus preceding the exanthem<sup>451</sup> which breaks out between the second and sixth days of the illness. It is rarely seen below the elbows and knees or on the face.<sup>452</sup>

The rather copious rash is like the typhus eruption at first maculopapular and red especially in the evening later it is petechial and even frankly purpuric especially in severe cases. The rash is followed by desquamation and pigmentation. The individual lesion measures 2 to 4 mm in diameter.<sup>453</sup> The rash may be extremely profuse<sup>454</sup> with hardly any normal skin left or it may be very sparse and even completely absent. It may appear in successive crops.<sup>455</sup> Hemorrhagic factors may cause the usually discrete lesions to coalesce into purpurae which may involve the entire body. Gangrene of the soft areas like the crinum or the soft palate may occur.<sup>456 457 458</sup> In abundant eruptions the skin is very tender. The distribution is a little different from typhus in that the rash most often<sup>459</sup> appears first on the flexor surfaces of the wrists<sup>460</sup> and ankles

<sup>446</sup>Johnson H. Rickettsiae in Frank beschaffen bei hämorrhagischem Fleckfieber (typhus exanthematicus). Arch. ch. 66: 6-62 1921. Zbl. 1 75.

<sup>447</sup>Brill N. F. A. Acute Infectious Disease of Unknown Origin. Am. J. Hyg. 129: 1-622 1917.

<sup>448</sup>Albright B. M. and Pullen R. L. Endemic Murine Typhus Fever. J. Hyg. 22: 425-436 1913.

<sup>449</sup>Parker R. R. Rocky Mountain spotted Fever. J. A. M. A. 119: 1185-1173 1917.

<sup>450</sup>Johnson H. L. spotted Fever Problem. Clinica 2: 890-913 1913.

<sup>451</sup>Topping N. H. Rocky Mountain spotted Fever. N. Ch. North America 27: 722-733 1917.

<sup>452</sup>Floyd M. L. Rocky Mountain Spotted Fever. J. Am. M. Soc. 27: 291-296 1917.

<sup>453</sup>Baker O. E. Rocky Mountain spotted Fever. Yearly study of Wyoming. Wyo. Journal-Lawyer 23: 207-213 1915.

<sup>454</sup>Baker O. E. Rocky Mountain spotted Fever. Ann. N. Y. Acad. Sci. 27: 217-260, 1915.

<sup>455</sup>Orr H. A. and Russell J. F. Rocky Mountain Spotted Fever. J. Pediatr. 27: 617-623 1916.



FIG. 73 - Rocky Mountain spotted fever. Severe case complicated by exanthematic dermatitis (the "not embedded" lesions in the skin of the neck and arms). (Courtesy Dr. G. E. Baker.)



FIG. 74 - Rocky Mountain spotted fever. Severe case complicated by exanthematic dermatitis (the "not embedded" lesions in the skin of the neck and arms). (Courtesy Dr. G. E. Baker, U. S. Public Health Service, Rocky Mountain Laboratory.)

spreading centripetally from there within two days <sup>872</sup> to the back, the arms, the legs and the chest, and finally to the abdomen where it is least pronounced. Palms, soles and face are involved last <sup>873</sup>. There is some relief of the muscular aches and pains after complete eruption.

Fig. 75.

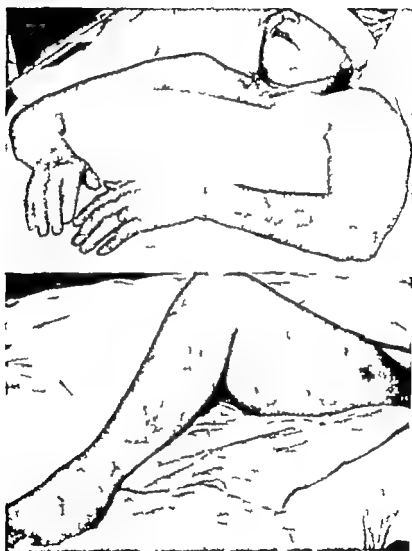


Fig. 76

Fig. 75 — Rocky Mountain spotted fever. Rash is petechial and of centrifugal distribution. (Arms. Courtesy Dr. G. E. Baker.)

Fig. 76 — Rocky Mountain spotted fever. Not greater distally toward the foot and purpuric spots on the thigh. (Arms. Courtesy Dr. G. E. Baker.)



Fig 77 - Rocky Mountain spotted fever. Dorsal rash on the hands. (Courtesy H. H. Baker)

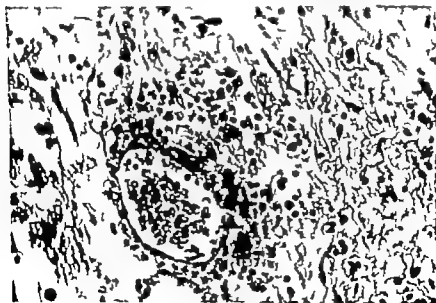


Fig 78. Rocky Mountain spotted fever skin lesions thirteenth day. Cell swelling of endothelial cells perivascular cuff. From Dr. R. D. Little. Pathology of Rocky Mountain Spotted Fever. U. S. Public Health Service.

No specific treatment has become recognized except hyperimmune rabbit serum which is useful only during the first days. Early removal of the tick may prevent infection. A specific vaccine from egg yolk culture is of prophylactic value.<sup>573</sup>

#### FIEVRE BOUTONNEUSE MARSEILLES FEVER OR FIEVRE EXANTHEMATIQUE ESCARRO-NODULAIRE

Fievre boutonneuse, Marseilles fever or fievre exanthematique escarro-nodulaire is a rickettsiosis of the Mediterranean areas. It is transmitted by a tick which feeds on dogs carrying the causative organism *Rickettsia conori*. The course resembles mild typhus, the mortality rate being less than 3 per cent. The rash is more papular than in typhus<sup>574</sup> and later often purpuric. Cases without eruption occur.<sup>57</sup> The rash starts on the trunk, legs and arms and involves the face last. The palms and soles are commonly involved, the abdomen staying relatively free. At the onset the tick bite is frequently visible as a lentil-sized shallow ulcer with a black necrotic center. This lesion is called *tache noire*.<sup>58</sup> It is of diagnostic importance but not always recognizable.

#### TSUTSUGAMUSHI DISEASE JAPANESE RIVER FEVER OR SCRUB TYPHUS

Tsutsugamushi disease, Japanese river fever or scrub typhus is a rickettsial disease of the west Pacific area. It is endemic in flooded areas and along rivers. The cause *Rickettsia orientalis* is transmitted by a mite which infests rodents, especially rats and a field vole.<sup>59</sup> According to Dyer<sup>60</sup> the disease takes a typical typhus course of about seventeen days' duration. The infecting bite causes a necrotic or scab-covered ulcer in about 75 per cent of the cases. The primary lesion is 2 to 10 mm. in diameter with an indurated red areola and is accompanied by a smooth, tender, nonsuppurative lymphadenitis which only rarely extends beyond the portal area.<sup>61</sup> The initial eschar is of diagnostic value. The rash which appears on the fourth day is noticeable only in about one-half of the cases<sup>62</sup> and is often preceded by a dusky flush on the face and neck.<sup>63</sup> It resembles that of spotted fever although Dyer<sup>64</sup> emphasizes the lack of hemorrhagic tendency. Characteristic eye ground changes and generalized peripheral lymphadenopathy are almost constant findings. The disease was known to have a fatality rate of 15 per cent, but in a recent series of sixty-four cases only 1.5 per cent of the patients died.<sup>65</sup> No specific therapy and no vaccine have been developed.

<sup>573</sup>Bollet, P. J. and Duran. Recherches nouvelles sur la fièvre exanthématique d'Alger méditerranéenne. Bull. Acad. de Méd. Paris 100: 914-950 1924.

<sup>574</sup>Ra, hand, A. Tache noire et fièvre boutonneuse. Bull. Soc. path. exot. 30: 625-627 1927.

<sup>58</sup>Blak, F. C. et al. K. F. Kadok, J. P. J. Hobbs, G. M. and Bell, E. J. Tsutsugamushi Disease, Scrub Typhus, Mite-Borne Typhus in New Guinea. Epidemiology (Medical Observations and Etiology) Vol. 11, pp. 41-54 1915.

<sup>59</sup>Shim, E. and Lipschutz, J. Tsutsugamushi Fever in the South-west Pacific Theater. J. A. M. A. 121: 1095-1100 1941.

<sup>60</sup>Macbeth, T. E. and Forrester, J. R. Tsutsugamushi Disease. Am. J. M. Sc. 210: 35 1943.

## TRENCH FEVER OR WOLHYNIA FEVER

Trench fever or Wolhynia fever a benign recurrent fever common among soldiers of World War I is caused by a rickettsia found in the epithelial cells of the stomach of the body louse.<sup>601</sup> The observations on the frequency of macular micropapular scarlatiniform or petechial rashes and of erythematous enanthemas vary widely <sup>573-582-583</sup>

## Carrion's Disease (Bartonellosis) Verruga Peruviana

In 1885 Daniel Carrion a Peruvian medical student, inoculated himself with blood and tissue from a lesion of verruga peruviana an eruptive disease occurring in certain South American valleys mainly in Peru. He died five weeks later of Oroya fever a clinically very different syndrome. This experiment strongly suggested the etiological identity of the two diseases which after much controversy has become generally accepted. The cause of both forms which may occur independently simultaneously or successively <sup>602</sup> is *Bartonella bacilliformis* a minute rod-shaped parasite of the red blood cells. Culture (Battistini after Fox<sup>603</sup>) and animal inoculation<sup>604</sup> have been successful <sup>604-605</sup>. The infection is transmitted by the sandfly *Phlebotomus verrucarum* the habitat of which corresponds to the few areas of endemic Carrion's disease. Fifteen to forty days after the infection the patient comes down with irregular fever malaise and anemia. If the disease takes the course of Oroya fever which has a mortality of 40 per cent the onset is sudden and the fever is at first continuous later remittant. The main feature is an acute severe anemia with a blood picture which resembles that of pernicious anemia. The red count may fall as low as 500 000. In addition there is a leukocytosis of about 20 000. Fox<sup>604</sup> remarks that there is probably no condition except hemorrhage which can cause severe anemia so quickly. The erythrocytes contain bartonellas in great numbers. Skin lesions are scanty. They are more numerous in the benign form called verruga peruviana which has the same incubation period but in which the fever and anemia are less severe.

The Spanish word verruga is used for all types of cutaneous excrescences and it should not be taken as a synonym for the dermatological term verruca. The characteristic lesions of the disease are nodules or tuberous masses which vary from pinhead to apple size and from a few usually large lesions to innumerable small efflorescences. One therefore speaks of millary and nodular forms, although there are many transitions. The rash comes on in crops and is itchy especially when it heals. The duration of the cutaneous form is variable on

<sup>601</sup>Jungmann, P. Das wolhynische Fieber Berlin 1919 Julius Springer

<sup>602</sup>Reichtrabstein A. Woth sieben Fieber oder Fünftagefieber Handb d inn Medizin, Vol I Berlin 1923 Julius Springer

<sup>603</sup>Miera B. Present Status of Human Bartonellosis, Bol Ofe sal panam 23: 301-309 1943 Abstr Trop Dis Bull 49: 901 1943

<sup>604</sup>Fox H. Verruga Peruviana—Personal Experience in Peru, J A M A 194 843-851 1923

<sup>605</sup>Jadassohn, J. and Arlitzky. I uber einen Fall von Verruga peruviana. Uebersetzung in Archiv f Hyg Infectiöskrankh 66: 247 1910

<sup>606</sup>De Rocha Lima H. Verruga peruviana oder Carrionische Krankheit (Oroya-Fieber) Handb d H. Gk 11: 1 218-212 1932



the average from four to six months (Odrizola<sup>667</sup>) The miliary verrugas appear quite symmetrically on the extensor surfaces of the limbs on the ulnar aspects of the hands and forearms,<sup>667</sup> and on the face The body the palms and soles and the genitalia usually remain free.<sup>668</sup> The individual lesion starts as a flat red hemorrhagic papule. There are subcutaneous and cutaneous lesions the depth explaining the variations in color The nodule grows so that at first a sessile and later a pedunculated bluish-red conical or hemispherical tumor on a base of ringlike pigmented folds results. The lesions are firm at first but soften later Small lesions look like senile hemangiomas.<sup>668</sup> The verrugas bleed easily If the verruga is at its height the surface is glossy a little moist and the color cherry red much like a fresh hemangioma or granuloma telangiectaticum. The verruga has a marked spontaneous healing tendency It may shrink or drop by atrophy of the base Bleeding is common and secondary infection occurs. Lesions in the mouth the nose and the conjunctivae have often been observed They have been found in the entire length of the gastrointestinal tract and on the serous membranes. These lesions may cause serious hemorrhages.<sup>667</sup>

Very large intracutaneous and subcutaneous sarcoid infiltrations of irregular shape may develop probably by coalescence of nodules. Large ulcerated granulomas are called *mulas* because the Peruvians believe that these big forms stem from infected mules. Infantile cases are usually mild.

The histological picture shows a sharply bordered vascular granuloma which consists mainly of endothelial cells (verruca cells) and inflammatory infiltration. There are many variations some suggesting sarcoma angioma or myxoma.<sup>664</sup>

Da Rocha Lima<sup>669</sup> and other authors found in the protoplasm of the verruga cells inclusion bodies which were considered to be an adaptation of the bartonellas to intracellular life.

The diagnosis rests on the unique dermatological aspect the history of a stay in a verruga area the fever and blood picture agglutination<sup>669</sup> and finally on the biopsy Leprosy and yaws must be ruled out.

<sup>667</sup>Odrizola, E. *La maladie de Carrion ou la Verruga Péruvienne*. Paris, 1908, Carré & Naud.

<sup>668</sup>Howe, C. Carrion Disease Arch. I : Med 72: 147 1912

## CHAPTER VIII

### SYSTEMIC INFECTIONS

#### Mycoses

Fungus infections are among the most common skin diseases but systemic mycotic infections are rare if one does not count the trichophytids.

#### COCCIDIOIDOMYCOSIS

The name coccidioidomycosis is preferable to coccidioidosis a term which may easily be confused with the protozoonosis, coccidiosis. The disease is endemic in dry dusty areas of some western states,<sup>60</sup> especially the San Joaquin Valley in Southern California<sup>61, 62</sup> where from December 1937 to May 1939 432 acute infections of San Joaquin Fever were registered. There is a peak of incidence in the fall. It is to the great merit of Dickson<sup>63</sup> to have shown that the acute respiratory infection known as San Joaquin Valley fever is the primary stage of coccidioidomycosis. The danger of such an endemic focus is illustrated by the fact that during recent military maneuvers in one of the endemic areas probably far more than the known seventy five cases occurred among several thousand soldiers.<sup>64</sup>

The cause is the fungus *Coccidioides immitis* which has a saprophytic hyphae phase and parasitic spherules or cysts which are double contoured refractile bodies which break up into radially arranged segments (endospores). In the infected person or animal these spores develop new spherules. The infection is mainly air-borne and but rarely occurs through the skin. The acute disease does not seem to be contagious from man to man as shown by the failure to infect even a bedfellow.

The air borne parasite causes a *primary lung infection* which probably often remains asymptomatic, but may manifest itself by severe chest pain irritating cough severe headache prostration and fever. The whole syndrome resembles influenza or pneumonia.<sup>65</sup> In rare instances a primary lesion is found in the skin.<sup>66</sup> A transient macular initial rash has been observed in some patients.

<sup>60</sup>Smith, C. E. Epidemiology of Coccidioidomycosis With Erythema Nodosum. Am. J. Pub. Health 23: 608-611 1930.

<sup>61</sup>Dickson, K. O. Primary Coccidioidomycosis: the Initial Acute Infection Which Results in Coccidioidal Granuloma. Am. Rev. Tuberc. 23: 711-722 1928.

<sup>62</sup>Smith, C. E. Coccidioidomycosis in CDM North America. 27: 780-807 1942.

<sup>63</sup>Goldstein, H. M. and Louis S. Primary Pulmonary Coccidioidomycosis. War Med. 4: 290-317 1943.

<sup>64</sup>Wass, W. A. and Johnson, O. H. Primary Coccidioidomycosis—Epidemiographic Study of Forty Cases. Ann. Int. Med. 17: 407-423, 1942.

<sup>65</sup>Kennel, J. F. Coccidioidomycosis. Am. J. Trop. Med. 21: 447-453 1941.



Fig. 79 — Erythema multiforme rash in systemic varicelliform virus (New Jersey fever). (Courtesy Dr. C. E. Smith)



Fig. 80 — Erythema multiforme rash in systemic varicelliform virus (New Jersey fever). (Courtesy Dr. H. P. Jarman)

Within the first three weeks of the acute respiratory phase erythema nodosum of typical distribution along the shins about the knees and on the lateral surfaces of the thighs, or erythema multiforme on the arms and occasionally on the face may break out. Goldstein and Louie<sup>43</sup> found an incidence of 25 per cent among infected soldiers all of whom probably were newcomers in the area but other percentages are much lower about 4 per cent.<sup>44</sup> Occasionally a morbilliform eruption has been noticed<sup>45, 46, 47, 48</sup> Severe arthritic pains, sometimes with swelling of the joints,<sup>49</sup> have given rise to the term desert rheumatism. Conjunctivitis is sometimes a feature of this stage Eosinophilia is a frequent finding Smith<sup>41</sup> stresses the appearance of erythema nodosum at the time the coccidioidin test becomes positive.

The prognosis of the primary acute febrile phase is good the mortality being less than 1 per cent After recovering from an attack of San Joaquin fever the patient usually remains in good health without further attacks. The coccidioidin test remains positive for a long time

The diagnosis of primary coccidioidomycosis is hardly made from the clinical picture alone although tuberculosis-like X ray changes in the lungs<sup>42</sup> with negative bacillary and allergic findings may suggest it. The history of having lived in an endemic area the finding of spherules in the sputum and a positive coccidioidin skin test secure the diagnosis. The cutaneous reaction becomes positive two to seventeen days after the onset of symptoms. In about 1 out of 1000 cases a progressive secondary granulomatous develops which is fatal in more than 50 per cent and may predominantly involve the respiratory tract the bones the central nervous system and least often the skin. Coexistence of lung foci in cases which clinically seemed to be restricted to the skin has been demonstrated at post mortem<sup>49</sup> Several clinical varieties of a severe dermatosis have been described. Jacobson<sup>50</sup> classifies the lesions into those of cutaneous subcutaneous and lymphadenitic origin The skin nodules which in their further development may invade the subcutis, are mainly found on the face, about the neck, and on the distal parts of the extremities. The nodules are painless, deep seated and pink to dusky red They occur in various sizes and shapes and finally ulcerate and exude a grayish yellow pus containing *Coccidioides immitis* From these dermic lesions, fungating papillomatous gran ulomas may arise creating a picture resembling mycosis fungoides. Widespread cutaneous lesions may heal with atrophic scars. Chronic sarcoid and lupus vulgaris-like pictures have been observed<sup>51</sup>

<sup>43</sup>Willett, F M and Weiss, A. Coccidioidomycosis in Southern California. Report of New Endemic Area, With Review of 100 Cases. Ann I Med 22 249 1 5

<sup>44</sup>Goldstein, H M and McDonald J B. Primary Pulmonary Coccidioidomycosis 78 Cases. J.A.M.A 121 537-541 1944

<sup>45</sup>Faber H K, Anik, O E and Dickson E H. Acute Coccidioidomycosis With Erythema Nodosum in Children (San Joaquin Fever). J Pediat 16 163-171 1939

<sup>46</sup>Dickson, E O. Coccidioides Infection. Ann Int Med 29 629 1937

<sup>47</sup>Rosenberg, E F, Dockert M B and Meyerding, H W. Coccidioidal Arthritis affected by Salicylamide and Roen gentherapy. Arch I Med 60 228-230 1 12

<sup>48</sup>Epstein, E. Prognostic Significance of Cutaneous Lesions in Coccidioidal Granuloma. Arch. Dermat. & Syph 35 783-83 1933

<sup>49</sup>Jacobson, H F. Immunotherapy for Coccidioidal Granuloma. Arch. Dermat. & Syph 40 821-840 1939

<sup>50</sup>Zelick, E P. Chronic Coccidioidal Dermatitis. Arch. Dermat. & Syph 26 82-71 1933



FIG. 81

Fig. 81.—Coccidioidal dermatitis. Verrucous papules. (From Zeller K. P. Arch. Dermat. 1933)

FIG. 82.

Fig. 82.—Chronic coccidioidal dermatitis, later stages resembling mastomycosis. (From Zeller K. P. Arch. Dermat., 1932.)

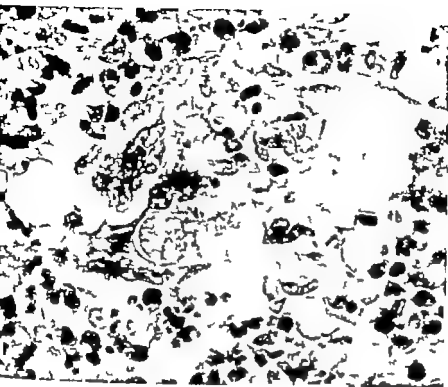


Fig. 34.



Fig. 33.

Fig. 33.—Chronic osteomyelitis of the mandible. Crossed, active lesions and anastomosing areas (From Keldner M. P. Arch. Dermat., 103:2.)

Fig. 34.—Chronic osteomyelitis of the mandible. Granuloma with giant cell containing spore-like cysts with capsule ruptured at one end. (From Keldner M. P. Arch. Dermat., 103:2.)

The appearance of acute milium pedunculated or *seem* dermic granulomas usually on the face is of ominous significance.<sup>403</sup> Their appearance is often preceded by symptoms of pulmonary or meningeal involvement. Such patients usually succumb to the coccidioidal infection in from six to twelve weeks after the appearance of the eruption. In some of these cases the fungus could be grown from the blood.

The course of the subcutaneous and lymphadenitic lesions is more chronic and relatively more benign. The subcutaneous granulomas are frequently the first cutaneous manifestations.<sup>404</sup> They start as soft frequently tender masses anywhere on the body and may form large flaccid tumors, cold abscesses and sinuses. If the flaccid tumor or abscess is surrounded by an extensive inflammatory infiltrate a hard gummatous lesion results. Finally just as in tuberculosis to which many clinical parallels exist specifically involved superficial lymphatic nodes may especially in the submaxillary region create scrophuloderma like lesions with abscesses, sinuses and scars.

The histopathology of the coccidioidal lesions is that of an inflammatory granuloma with marked tuberculoid tendencies. There is edema and a diffuse cellular infiltrate predominantly composed of lymphocytes, epithelioid and giant cells of the Langhans type. These giant cells harbour the coccidioidal spheres which have been demonstrated in the process of rupturing and releasing the spores.<sup>405-407</sup>

The treatment is still unsatisfactory. Jacobson<sup>401</sup> who has had wide experience with coccidioidomycosis reviewed in 1939 the many methods of treatment. Intravenous injections of a 1 per cent solution of antimony and potassium tartrate.<sup>404</sup> Intramuscular injection of colloidal copper, oral administration of potassium iodide, arsenic or combinations of these agents and roentgen therapy have not given convincing results. Jacobson<sup>401</sup> now feels that immunizing therapy is superior to the chemotherapy known so far and has had 20 per cent good results (personal communication). The patients are in intervals of one to two weeks given intravenous injections of vaccine starting with 0.05 c.c. and increasing by 0.05 c.c. each time. A course consists of twelve injections. Between the courses is a rest period of six to eight weeks.<sup>408</sup>

### TORULOSIS

Only a few cases of systemic infection with the yeastlike fungus *Torula histolytica* (*Debaryomyces neoformans*) are known. Tuberculosis resembling granulomas in the brain, the lungs, the gastrointestinal tract and other organs is the outstanding feature of the disease. The comprehensive monograph of

<sup>403</sup> E. A. N. and Hall, H. A. Coccidioidal Granuloma—50 Cases. J. A. M. A. 83: 1881, 1929.

<sup>404</sup> W. H. and Jacob, F. M. Granuloma Coccidioides, Arch. Dermat. & Syph. 16: 309, 1927.

<sup>405</sup> E. A. N. and Kimura, F. Skin Test for Coccidioidal Infection. J. Infect. Dis. 66: 212.

Stoddard and Cutler<sup>626</sup> emphasized the *lack of skin manifestations*. Since then a few cases with dermatomes have been reported.<sup>627-628</sup>

Acneiform pustules, granulomatous ulcers and deep-seated abscesses nodules or plaques<sup>629</sup> varying from almond to hand size without ulcerative tendency have been observed. The histopathologic characteristics of cutaneous torulosis include tuberculoid granulomas with caseation and enormous numbers of giant cells containing the double-contoured oblong or spheroid refractile organisms. There exists a close similarity between torulosis and coccidioidomycosis.<sup>631</sup>

### BLASTOMYCOSIS

H Montgomery<sup>631</sup> complains about the loose use of the term blastomycosis. He suggests that the word should be used only for the disease described by Gléchrist<sup>632</sup> in 1896 and not for all infections caused by yeastlike organisms.



Fig. 35 — Blastomycosis. Primary lesion of neck resembling verrucous

The American blastomycosis is caused by the yeastlike fungus *symonema dermatitidis* which can be demonstrated in the pus or in the tissues as a refractile double contoured budding round organism often appearing in unequal pairs.

- <sup>626</sup>Stoddard J. L. and Cutler E. C. Toruli Infection in Man. Monograph 6, New York, 1916, Rockefeller Institute for Medical Research.  
<sup>627</sup>Urban E. and Zach F. Generalisiert Torulose (europäische Blastomycose). Arch. f. Dermat. u. Syph. 1922 401-42 1926.  
<sup>628</sup>Rappaport, H. E. and Kaplan D. Generalized Toruli Mycosis, Arch. Path. 2 720, 1936.  
<sup>629</sup>Wickman, F. D. Cutaneous Torulosis. Sex. 5 31 J 25 231-252 1922.  
<sup>630</sup>Wick U. J. Cutaneous Torulosis. Arch. Dermat. & Syph. 21 24-26 1922.  
<sup>631</sup>Montgomery H. A new American Blastomycosis. M. Clin. North America 19 641-652, 1930.  
<sup>632</sup>Gléchrist T. C. Blastomycotic Dermatitis. Johns Hopkins Hosp. Rep. 5: 267, 1896.



## PLATE I

- 1 Acute septicemia. Bullous rash with hemorrhagic component. Fatal outcome.
- 2 Acute septicemia. Purpuric bullous rash.
- 3 *Leptus vulgaris* plaques. Not brownish spot under glass pressure.
- 4 Tubercular ulcer of the tongue | pulmonary tuberculosis. (Case of Dr. J. Goodman)
- 5 Systemic blastomycosis. Progressive skin lesion.
- 6 Systemic blastomycosis. Progressive and stable lesions.

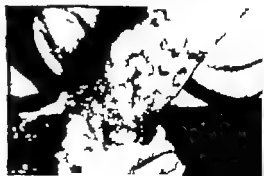


PLATE 1



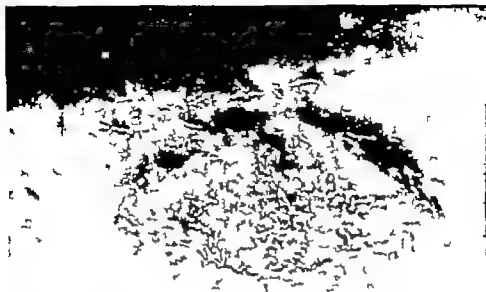


Fig 55.—*Eleutheromyces*. Leg lesion. Note bulging edge with small abscesses. In the periphery of these abscesses one is likely to find the yeasts



Fig 57.—*Eleutheromyces*. Small skin lesion in systemic infection

The organism grows well on the usual fungus media where it develops mycelia which are not found in the lesions.

Blastomycosis may occur as a primary skin infection and in the majority of the cases it remains a dermatosis. A fraction of the skin cases may become systemic and involve other organs setting up internal foci which may metastasize and thus secondarily involve the skin.<sup>62</sup> The widely scattered subcutaneous rather indolent nodules may develop slowly into cold abscesses which may reach large size. The even and symmetric distribution of nodules and abscesses and their frequent involvement of the covered parts in contrast to the ectogenous lesions which favor the face arms and hands, indicate their hematogenous pathogenesis. The abscesses may form ulcers and sinuses from which typical blastomycotic skin lesions may arise.



Fig. 88 — Blastomycosis. GORDON-HILL. Large pyogenic lesion.

The primary skin lesion of blastomycosis is a papulopustule which slowly grows peripherally. Within a few months it forms<sup>63</sup> a coin-shaped thick, firm elevated patch the surface of which is papillary or verrucous and often fissured or lobulated. The center becomes depressed as soon as the lesion has reached the size of about a half dollar. The most characteristic feature is the steeply raised succulent red border in which many pin point to pinhead sized abscesses are contained. By means of pressure and a magnifying glass they can easily be made visible. The small quantity of pus which can be expressed from these tiny abscesses is the best material for microscopic study and culture. These lesions may by growth and coalescence attain large size and even cover entire regions. The center of such large lesions is often scarred but there are active foci scattered throughout the scar tissue in varying density. The active foci in old lesions are often crusty oozing with serum and pus and apt to bleed on the slightest touch. The destructive power of such large blastomycotic granulomas

<sup>62</sup>Gordon O. and Montgomery H. *Diseases of the Skin*. Philadelphia, 1913. Lea & Febiger.

is great. Prominent soft parts for example the scrotum<sup>80</sup> the alae nasi and the lids may suffer great damage. The polycyclic border of old lesions remains more or less papillary often cordlike. The scarring does not always keep pace with the extension of the lesions so that large areas may remain thickly covered with red beds of vegetating masses. In other cases the peripherally progressing border leaves in its wake a smooth red ulcerative area almost devoid of any healing tendency.



Fig. 96. Usually severe systemic blastomycosis. This type of blastomycotic lesion resembles tuberculous cutis verrucosa. This case healed after three months of treatment. (His iodine and x-ray). (From Bush, J. D. Arch. Derm. 1:1.)

In 50 per cent of the systemic cases the first symptoms are referable to the respiratory tract. The picture may resemble that of a cold or of an attack of influenza. In 4 per cent the primary lesion followed an injury. In 19 per cent a skin lesion was noted first and in 23 per cent the earliest lesion was a subcutaneous nodule or abscess often on unexposed parts.<sup>81</sup> Besides a great variety

<sup>80</sup>Martin, D. and Smith, D. T. Blastomycosis. Review of Literature, Am. Rev. Tuberc. 29: 273-304, 42-512, 1929.

of occasional organic involvements the bones mostly the vertebrae and joints, become infected in about 50 per cent of the systemic cases.

The histopathology reveals a granuloma with varying mixtures of leukocytes lymphocytes plasma cells and Langhans type giant cells which often contain some fungus elements. Tubercle formation is not marked.

Enormous acanthosis and millary abscesses throughout the hypertrophic rete as well as the corium are characteristic features.

The reservoir of the infecting fungus is probably on certain plants. Infection from man to man occurs only under extraordinary circumstances. The only such case known is that of a physician who injured himself at the necropsy of a case of systemic blastomycosis (Evans after Martin and Smith<sup>62</sup>).

The age incidence has its peak between 20 and 40 years. Men are nine times as often infected as are women. The disease is far more common among the poorer classes.<sup>63</sup>

The prognosis of the systemic cases is almost invariably fatal. The localized primary skin infection may take a chronic course but it will finally heal unless it becomes systemic, which is unusual.

Clinical diagnosis from the skin lesions is often possible. Other mycoses tuberculosis verrucosa syphills and fungating granulomas must be ruled out. The detection of the organism in the pus of small abscesses microscopically or by culture will usually confirm the clinical diagnosis. For the microscopic examination the material is covered with a drop of 40 per cent KOH and examined in minimal light after at least ten minutes. A vaccine from heat killed fungi<sup>64</sup> is used in the diagnosis and treatment.

**Treatment.**—Excision of small lesions may occasionally arrest the disease. Irritating substances such as caustics often make the condition worse. Potassium iodide in huge doses up to 25 Gm. daily<sup>65,66</sup> has often healed and often failed but it is nevertheless still the method of choice. Combination with X ray therapy and vaccine may be judiciously used in combination with potassium iodide which loses its effect after prolonged administration. Martin and Smith caution against the indiscriminate use of potassium iodide in hypersensitive cases. These cases should be desensitized by a series of vaccine injections.

## CHAPTER IX

### HELMINTHIC DISEASES

#### Trichinosis

It is now well established that trichinosis is a common human infection in the United States. A great number of post mortem diaphragm examinations conducted in various parts of the country<sup>836-840</sup> have shown that 12 to 18 per cent of the cadavers harbor trichinae. The infection stems largely from inadequately cooked pork rarely from the meat of bears, wild boars and some other large animals. A main source of infection of the swine is the practice of feeding them uncooked scraps of pork, while trichinous rats play a minor role.<sup>841</sup> On ingestion of trichinous meat the dormant and encysted worms are freed by the gastric juice. They propagate in the small intestine after one week. The young worms which are smaller than a red blood cell are carried by the circulation to the muscles. Here they grow and encapsulate and may live for as many as thirty years.

The clinical picture of human trichinosis depends on such factors as massive infection or small size of the patient, tissues invaded, general resistance and concomitant pathological conditions.<sup>842</sup> Many cases pass symptomless or undiagnosed. The clinical course can be divided roughly into three stages (Davaene after Beeson<sup>843</sup>) but it must be emphasized that this clearly defined sequence is seldom observed in practice. There is an initial gastrointestinal phase starting sometimes hours after the ingestion of trichinous meat. At the end of the first week, it is followed by a stage of dissemination marked by prostration, facial edema, fever, sweating and pain in the muscles of respiration, mastication and the eye. After six weeks the disease passes gradually into the stage of encystment of the worm in the muscles while the severe symptoms ease up and the fever subsides. Edema, muscular pains and anemia may persist for a long time. The average mortality which was very high in some German epidemics of the nineteenth century is probably less than 5 per cent of the clinical cases in the United States.<sup>844</sup> Most deaths occur from the fourth to sixth week and are due to myocarditis or bronchopneumonia.<sup>845</sup> There are indications that existing infection protects against reinfection.<sup>846</sup>

<sup>836</sup>Hall, M. C. and Collins, B. J. Studies on Trichinosis, Pub. Health Rep. 62: 488-490, 1937.

<sup>837</sup>Hall, M. C. Studies on Trichinosis, Pub. Health Rep. 62: 529-531, 1937. 53: 1472-1495, 1938.

<sup>838</sup>Kerr, E. B., Jacobs, L. and Cuvillier, E. Trichinosis: Post-mortem Examination of 8,000 Diaphragms From Washington, D. C. and Five Eastern Seaboard Cities, Pub. Health Rep. 64: 826-833, 1941.

<sup>839</sup>Geard, S. E. Trichinosis, Springfield, Ill., 1943, Charles C. Thomas, Publisher.

<sup>840</sup>Gould, H. E. Method for Control of Trichinosis in the U. S. A. J. A. M. A. 123: 1241-1244, 1944.

<sup>841</sup>Beeson, P. B. Trichinosis—Clinical Manifestations, Lancet 1941: 2: 47-50.

<sup>842</sup>Davies, O. Trichinosis, Connecticut M. J. 4: 314-317, 1940.

<sup>843</sup>Wyrnos, R. O., Trench, J. H., and Nagath, T. B. Trichinosis, J. A. M. A. 117: 423-433, 1941.



The blood changes are characteristic. There may be severe anemia and leukocytosis. *Eosinophilia* is an almost invariable sign in the second stage. It may range from a few to 73 per cent<sup>644</sup> and is considered the most reliable diagnostic sign.<sup>645</sup> However eosinophilia may be missed or disappear in severe cases.<sup>646</sup>

A cutaneous *immediate urticarial reaction* with an allergen from digested trichinous meat has been developed by Bachman.<sup>647</sup> Besides the immediate response which appears within thirty minutes a *delayed* reaction may occur after two days. This test is supposed to become positive in the third week of illness.<sup>161-417-448</sup> The reaction is about as reliable as the precipitin reaction which becomes positive in the fourth week<sup>649</sup> or as the complement fixation test.<sup>650</sup> Considering the frequency of trichinella infection a positive skin reaction is only valuable if supported by other evidence of recent infection or if it has turned positive while the disease has been observed.<sup>130</sup> The test<sup>6</sup> may be negative in very severe cases.<sup>134-403-402</sup> In all tests group reactions against other common worm infections must be borne in mind.<sup>651</sup> For example Fülleborn<sup>652</sup> mentions a case of a patient infected with echinococcus who gave a positive reaction to echinococcus antigen as well as to antigen from *Cysticercus tenuicollis* trichinella and strongyloides. There is also a common antigen in ascari and trichinella<sup>134</sup> and pinworm and trichinella.<sup>653</sup> Muscle biopsy (gastrocnemius) is rarely necessary. The muscle specimen should be pressed between two glass slides and examined at low power as is done in the testing of meat. Trichinae can occasionally be centrifuged from the stools the bile the arterial blood<sup>654</sup> or the cerebrospinal fluid.<sup>655</sup>

**Dermadromes.**—The scarcity of cutaneous lesions is in agreement with the rarity of the presence of trichinae in the skin of experimentally infected mice.<sup>656</sup>

**Edema of the eyelids** is the most common and in fact the only dermadrome which is seen in the majority of the cases. It is an early important sign of mus-

<sup>644</sup>The allergen can be obtained from the National Institute of Health in Bethesda, Md. It is also done the precipitin test on serum sent in for this purpose.

<sup>645</sup>Harphay F D James H D and Rastetter J W. Trichinosis 23 Cases. Am J M Sc 199 323-328, 1940.

<sup>646</sup>McNaught J B. Laboratory Procedures for the Diagnosis of Trichinosis, Am J Clin. Path Tech Sect B 67-93 1944.

<sup>647</sup>Bachman O W. An Intradermal Reaction in Experimental Trichinosis, J Prev Med 2: 813-833 1937.

<sup>648</sup>McNaught J B. Diagnosis of Trichinosis, Am J Trop Med, 19 161 1937, 1938.

<sup>649</sup>Hall A A. Trichinosis. Use of the Bachman Intradermal Skin Test. Ann Int Med 19: 1544-1550, 1937.

<sup>650</sup>Kaufman R E. Trichinosis. Clinical Considerations, Ann Int Med. 12 1421 1460 1940.

<sup>651</sup>Gazze A. Trichinosis. Serodiagnosis With Complement Fixation. Meehan and Wehncke 23 473-474 1941.

<sup>652</sup>McNaught J B. Medical and Public Health Aspects of Trichinosis, Texas Stat J Med 29: 223-235 1942.

<sup>653</sup>McNaught J B Beard R H and Myers J D. Diagnosis of Trichinosis by Skin and Precipitin Tests, Am J Clin Path 11 196-201 1941.

<sup>654</sup>Jadassohn W. Die Immunbiologie der II. Handb d III. Ok 2 41 1932.

<sup>655</sup>Fülleborn F. Diagnostik. Cutaneale Kon bei Helminthenkrankheiten, Klin Wchnsch 7 230, 1922.

<sup>656</sup>Dammin H J. Trichinosis—Report of Case With Demonstration of Larva in Arterial Blood. New England J Med 224 287-290 1941.

<sup>657</sup>James E A and Ott O F. Occurrence of Trichinella Spiralis Larvae in Tissues Other Than Skeletal Muscles, J Lab & Clin Med 27 1244-1247 1942.

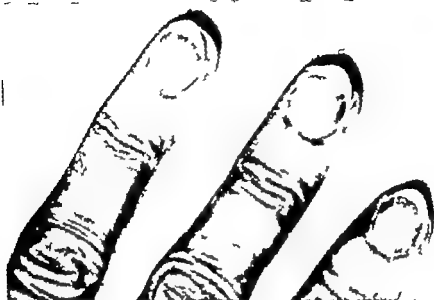


Fig 90.—Splinter hemorrhages in trichinosis (Courtesy Dr Knight, J. B. Am J Trop. Med., 1929.)

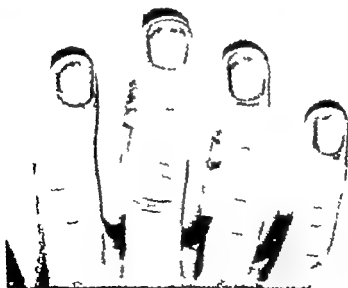


Fig 91.—Trichinosis splinter hemorrhages arranged in cross like index, ring simultaneous growths (courtesy Dr Brown)

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<sup>640</sup>The allergen can be obtained from the National Institute of Health in Bethesda, Md. which also does the precipitin test on serum sent in for this purpose.

<sup>641</sup>Starup, P. D. James, H. E. and Rastet, C. J. W. Trichinosis. *Et Casus*, *Am J. St. Sc.* 199: 228-234 1940.

<sup>642</sup>St. Vaughn, J. B. Laboratory Procedures for the Diagnosis of Trichinosis. *Am J. Clin. Path. Tech. Sect. B* 7-43 1944.

<sup>643</sup>Bachman, G. W. An Intradermal Reaction in Experimental Trichinosis. *J. Prev. Med.* 2: 513-523 1933.

<sup>644</sup>McNigh, J. B. Diagnosis of Trichinosis. *Am J. Trop. Med.* 19: 181-182, 1929.

<sup>645</sup>Had, A. A. Trichinosis. Use of the Bachman Intradermal Skin Test. *Ann. Ent. Med.* 18: 1814-1850 1937.

<sup>646</sup>Lawrence, R. K. Trichinosis. Clinical Considerations. *Ann. Int. Med.* 18: 1421-1480, 1940.

<sup>647</sup>Osase, A. Trichinosis. Serodiagnosis With Complement Fixation. *Mitchell and Wehner* 22: 473-474 1941.

<sup>648</sup>St. Vaughn, J. B. Medical and Public Health Aspects of Trichinosis. *Trans. Stat. J. Med.* 23: 252-255 1942.

<sup>649</sup>St. Vaughn, J. B., Heard, R. R. and Myers, J. D. Diagnosis of Trichinosis by Skin and Precipitin Tests. *Am J. Clin. Path.* 11: 83-90 1941.

<sup>650</sup>Jadavjee, W. Die Immun-Nekrose der Haut. *Handb. d. H. u. S.* 18 1932.

<sup>651</sup>Fülleborn, F. Diagnostische Anzeichen bei Helminthosenkrankheiten. *Klin. W. u. w. 7*: 130 1928.

<sup>652</sup>Danzon, J. Trichinosis. Report of a Case With Demonstration of Larvae in Arterial Blood. *New Zealand J. Med.* 23: 247-260 1941.

<sup>653</sup>Masson, K. A. and F. Occurrence of Trichinella spiralis Larvae in Tissues of the Thorax. *Br. J. Pathol. Bacteriol. J. Lab. & Clin. Med.* 22: 2: 247 1942.

# Ancylostomiasis (Hookworm Disease)

**Ancylostomiasis (Hookworm Disease)** The hookworms<sup>884</sup> for medical purposes the genera *ancylostoma* and *necator* are duodenal human parasites whose larvae leave the bowel with the feces in great numbers. These larvae are about 0.5 mm. long. They enter the body through the unbroken skin especially the thin skin of the instep area and are carried by the lymph and blood to the lungs from where they follow the bronchotracheal tree into the larynx pharynx, and finally the gastrointestinal canal (Loose after H. Bruns<sup>885</sup>) to their living and breeding place the duodenum. The hookworms are found chiefly in warmer climates. They have caused epidemics in warm countries among barefooted workers on rice, tea, mulberry and similar plantations and in colder climates among miners working in the warm and humid shafts.

The disease is common in the southern section of the United States and especially in Puerto Rico. The infection causes a severe often fatal progressive anemia and involvement of many organs.

**Dermadromes**—When the larvae penetrate the skin of the feet they cause itching vesicular dermatitis and possibly secondary infection. However a controversial point is to what extent hookworm causes the ground itch of the south or mazamorra of Puerto Rico and Central America a common eczematous condition of the feet. Fülleborn<sup>886</sup> denies that the majority of the ground itch cases have anything to do with ancylostomiasis. It is claimed that *Necator americanus* is more likely to cause ground itch than *Ancylostoma duodenale*.<sup>887</sup>

If the hookworm infection has become fully developed *pruritus* marked *dryness* of the skin and hair reduced perspiration on exertion and heat and *burning of the palms* are reported to be troublesome symptoms (Ashford and King after Fülleborn<sup>888</sup>). The features are reported to become blurred and slightly puffy shift of pigment takes place<sup>889</sup> and persistent acne may occur. A butterfly-shaped pigmentation over the bridge of the nose has at times been thought to be diagnostic of schistosomiasis but this is not true since such pigmentations occur also in other infections (bilharziosis) and probably also in various nonhelminthic conditions. The diagnostic value of minute black or brown spots on the side of the tongue or on the lips in patients with hookworm is doubtful.<sup>887,890</sup>

**Crawling eruption**: caused by the larvae of *ancylostoma braziliense* and other nematodes, is not always restricted to the skin.<sup>889,891</sup> It may like other worm

<sup>884</sup>Fülleborn F. Hart and Heinsdethen Handb. d. H. u. Gk. 22.1 706-800, 1922.

<sup>885</sup>Bruns, H. Die Ancylostomiasis in der gesamten Zone Handb. d. path. Mikrocorg. 6, 2 907-918, 1929.

<sup>886</sup>Darwinian, O. Die Ancylostomiasis der Tropen und Subtropen. Handb. d. path. Mikrocorg. 6 2 949-994 1929.

<sup>887</sup>Butler, R. L. and Sutton R. L. J. Diseases of the Skin, St. Louis, 1930 The C. V. Mosby Co.

<sup>888</sup>Jochers, H. Pigmentation of the Skin. New England J. Med. 231 88-100, 122-126, 181 199 194.

<sup>889</sup>Milneburgh, J. A. and Sompayras L. M. Hookworm Infection, Crawling Eruption. Infection With Ancylostoma Braziliense U. S. N. M. Bull. 60 293-306, 1943.

<sup>890</sup>Kirby-Smith, J. L. Dove W. E. and White, G. F. Crawling Eruption. Arch. Dermat. & Syph. 12 137 178, 1926.

infestations and some bacterial infections be accompanied by transient and migratory pulmonary infiltrations with few or no symptoms. This is known as *Loeffler's syndrome*<sup>671</sup>

### Ascariasis

Infestation with large roundworms has been held responsible for a number of dermatoses. It is certain that ascarides contain a highly sensitizing allergen which may explain cases of urticaria angioneurotic edema pruritus nam epistaxis, and eczema. The same precaution as is used in the evaluation of allergic tests in other worm infections (see under trichinosis) must be used in the skin tests for ascarides.<sup>668 664-671-672</sup> The possibility of anaphylactic shock with asthma and urticaria in repeated intracutaneous tests with ascaris antigens is emphasized by several authors.<sup>673</sup> Another difficulty is that at least in some areas for example the southeastern parts of the Appalachian range<sup>644</sup> the incidence of a sensitization to ascaris is so widespread among the population that the test loses its diagnostic value.<sup>674</sup> The pathogenesis of some skin lesions for instance pruritus and eczema of the hands itching of the nose and bullous or acneiform eruptions<sup>675</sup> may be explained by local reactions to the worm allergen in ova carried and inoculated by the hands. Several observers have expressed the thought that the itching and scratching of the nose in worm infestation which is so common in the tropics is an important cause of the first infection with leprosy.

### Oxyuriasis

Similar conditions of allergy combined with the mechanically caused itching produced by the migrating worm exist in pinworm (*Enterobius* or *Oxyuris vermicularis*) infestation. The worms<sup>676</sup> live in the lower ileum and cecum but descend to the rectum for egg laying. From there they may at night reach the anus and occasionally distant skin areas. Scratching and inoculating of the crushed worms or eggs may cause local allergic reactions.<sup>677</sup> Neurodermatitis which responded to anthelmintic treatment and flared up on injection of oxyurus extract has been described.<sup>78</sup> Biting of the nails sucking of the thumb and picking at the nose often considered suggestive of worm infection were found no more frequently in infested persons than in control groups.

<sup>671</sup>Wright D. O. and Todd E. M.: Loeffler Syndrome Associated With Creeping Eruption, *J. A. M. A.* 128: 1042-1043 1943

<sup>672</sup>Agaci H.: Die Cutiraction bei Ascaris l. subricolles, Istanbul Peritrya (N. 4) 75-78, 1937 *Erl.* 88: 430

<sup>673</sup>Schickel W.: Ascariden reaktion und All. *Arch. f. Dermat. Syph.* 87: 81-70 1937

<sup>674</sup>Dickel F. and Schworze P.: Allergie der menschlichen Haut gegen Ascaris lumbricoles, *Arch. f. exper. Path. Pharmacol.* 28: 376 1936

<sup>675</sup>Arbitts J.: Helminthen bei H. krauskel en und ihre Behandlung, *Dermat. Wechnscr.* 89: 297 1923

<sup>78</sup>Cram, H. B.: Oxyuriasis, *Am. J. Dis. Child.* 85: 46-69 1943

<sup>676</sup>Wojcicki P. K.: Histreaktionserche mit Helminthoprodukten bei Kindern, *Monatsschr. f. Kinderk.* 89: 61-71 1934

<sup>677</sup>Schrödl, E.: Neurodermatitis durch Oxyurus, *Dermat. Wechnscr.* 83: 1052-1057 1936

The diagnosis rests on the finding of worms or their ova. The latter are best collected with a few energetic strokes in a peripheral direction from the anus, with a cellophane (Scotch tape) tipped swab.<sup>379</sup> The cellophane is then examined on a slide moistened with water and covered with a cover slip. A skin test with enterobius antigen may be helpful.<sup>379,410</sup> Brady and Wright<sup>421</sup> were unable to find any typical cutaneous lesions in 200 controlled cases. In a series of tests, Brady and Wright<sup>401</sup> found that gentian violet given by mouth was superior to other methods. The dosage of the drug for adults was two 32 mg tablets three times a day before meals, and for children 10 mg a day for each year of their apparent not actual age the total amount being divided into three doses.

### Filariasis

*Wuchereria (Filaria) bancrofti* is a nematode of the warm climates. The adult worm which is as thick as a strong hair and several centimeters long lives in the human lymphatics and produces tremendous numbers of microfilariae which are about 0.3 mm. long and no thicker than a red blood cell. These microscopic worms live in the blood appearing in great numbers at night in the peripheral blood and retreating at day into the visceral arteries. The microfilariae pass part of their development in various mosquito vectors, but they are brought back into man to complete their life cycle. According to Manson Bahr,<sup>422</sup> Fülleborn<sup>423</sup> and other authorities on tropical medicine the microfilariae in spite of their number have no pathogenic properties while in a certain proportion of instances the obstruction of lymphatics caused by the adult worm causes lymphedema, lymphatic varicosities and elephantiasis. The monstrous enlargements of legs, mammae, scrotum and other parts are well known pictures of tropical pathology. The lymphatic inflammatory reaction, scarring and calcification caused by the adult worms may be permanent. The lesion is likely to become infected with hemolytic streptococci causing the repeated erysipelatoid attacks which are the more immediate cause of elephantiasis.<sup>402,424</sup> Other authors believe that elephantiasis may develop without acute attacks.<sup>424</sup> Grace<sup>425</sup> feels that there is no evidence that *Wuchereria (Filaria) bancrofti* plays any part in the production of the attacks of lymphangitis. Recent observations on military personnel in endemic areas<sup>426</sup> have shown that acute lymphangitis of arms or legs and acute funiculitis or epididymitis with little fever or general symptoms are the outstanding early clinical symptoms. Peculiar features are a centrifugal lymphangitis which may work down from the

<sup>379</sup>Witali M. C. Studies on Oxyuriasis. I. Types of Anal Swabs and Scrapers. *Am J Trop Med* 17: 4 5-423 1937

<sup>380</sup>Tsuchiya, H. and Banerjee T. C. Intradermal Test as Aid in Diagnosis of Enterobiasis. *J Lab & Clin Med* 24 627-631 1930

<sup>381</sup>Brady F. J. and Wright W. H. Oxyuriasis, 300 Cases. *Am J M Sc* 190: 267-272. 1908

<sup>382</sup>Low H. C. Pathology of Filariasis. *J Nat Med* 29: 394-395 1921

<sup>383</sup>Ding S. L. Filariasis and Elephantiasis. *Nederl tijdschr Geneesk* 78 2772-2776 1932

<sup>384</sup>Eid 42 1-4

<sup>385</sup>Kelback, L. Clinical Studies of Filariasis. *Nederl tijdschr Geneesk* (edid 72: 847-848 1932

<sup>386</sup>Grace A. W. Filariasis, Tropical Lymphangitis and Abscesses. *J A M A* 133: 405-408, 1943

<sup>387</sup>Thompson, K. J. Rifkin H. and Zarow M. Early Filariasis in Young Soldiers. *J.A.M.A* 136: 1074-1080, 1943



Fig. 92—Microfilariae of *L. loa* in blood film (X1700). Actual length 166 microns. The only successful preparations were made from the blood taken from Calabar swelling on the forearm in the late afternoon. Giemsa stain. (From Guy W. H. Cohen, M. and Jacob F. M. Arch. Dermat., 1943.)



Fig. 93—Calabar swelling. From G. W. H. Cohen, M. and Jacob, F. M. Arch. Dermat. 1943.)

upper arm to the wrist and lymph nodes in unusual sites for example the tip of the ileum the midarm and the region of the serratus and teres muscles. Centripetal lymphangitis occurs also. In the chronic stages the skin manifestations are due mainly to the enormous lymphatic varicosities and enlarged lymph nodes which may cause dome-shaped pseudovesicles of the skin. A positive reaction to an intradermal injection of 1:4000 *filaria antigen* is considered diagnostic.<sup>66</sup> Other worm infections do not respond to a dilution higher than 1:2000. *Filaria loa*, an African species transmitted by a fly, migrates in the connective tissue, often near or in the skin or beneath the bulbar conjunctiva producing the so-called *Calabar swelling*; these lesions appear on the forearms or less commonly over the ankles or on the face. They probably represent an allergic

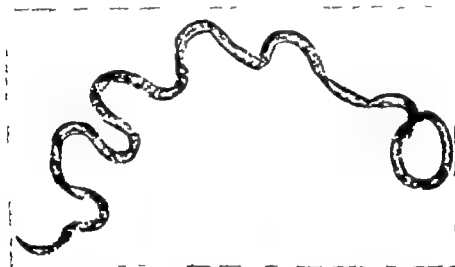


Fig. 91.—*Filaria* of *L. loa* (X6) actual length 40 mm. Adult worm removed from the conjunctiva of missionary returned from the Cameroons, Africa. Note the aclear structures and the twist at the caudal end. (From G. J. W. H. Cohen M., and Jacob, P. M. Arch. Dermat. 1943.)

reaction to the worm or its products. The worm or calcified remnants of it have been demonstrated by roentgenogram.<sup>667</sup> The swellings are usually rather painless but sometimes itchy. They disappear after a few days or rarely after weeks,<sup>668</sup> only to recur somewhere else.<sup>669</sup> Scabies-like itching eruptions are known as filarial prurigo or gale filarienne.<sup>700</sup> Besides the mentioned skin tests, complement fixation reactions in filariasis have been developed.<sup>699-700</sup> Eosinophilia may reach 24 per cent.<sup>699</sup>

<sup>667</sup>Orris E. D. W. Filariasis, Cause of Calabar Swelling With Radiologic Observations, J. Trop. Med. 43: 19-21, 1940.

<sup>668</sup>Ouy W. H. Cohen, M. and Jacob, P. M. Infection With Loa-Loa, Arch. Dermat. & Syph. 67: 763-767, 1943.

<sup>669</sup>Atchafopoulou, G. J. Filarial Prurigo or Gale Filarienne in Case Due. Loa-Loa. Trop. Dis. Bull. 40: 322, 1943.

<sup>670</sup>Fairley N. H. Skin Test and Complement Fixation in Filariasis, Tr. Roy. Soc. Trop. Med. & Hyg. 28: 230-231, 1932.

<sup>671</sup>Kodak, J. and Debats, A. Intradermal Reactions in Human Filariasis, Tr. Roy. Soc. Trop. Med. & Hyg. 28: 377-382, 1933.

<sup>672</sup>Low G. C. Skin Conditions Found in Loa-Loa Infections, J. Trop. Med. 37: 350-360, 1934.



An eosinophilic disease with migratory edematous swellings which has lately been observed in small epidemics in Palestine probably is related to Calabar swelling<sup>402</sup>

### Onchocerciasis

*Onchocerca* is a nematode which resembles filaria in many respects. The life cycle which is not fully understood is partly spent in flies of the genus *Simulium*. The adult worms and great numbers of microfilariae live in cystic tumors (onchocercomas) of the subcutis. The majority of the patients with onchocercomas present no demonstrable cutaneous manifestations. However microfilariae have been found in great numbers in apparently unaffected skin<sup>403</sup> as well as in the blood. The onchocerca nodules are pea to almond-sized and occur most frequently over the skull which they may perforate along the costal arches and about the joints where they may simulate juxta articular nodes. There is an African type caused by *Onchocerca volvulus* and a Central American type caused by *Onchocerca cercaricus*. The latter is restricted to parts of Guatemala and Mexico. The American onchocerciasis is of importance because of the keratitis and iritis which accompany many cases and which may lead to blindness (onchophthalmia)<sup>404-406</sup>. Acute febrile erysipelatoid swellings of the face and of the limbs characterized by hardness and a greenish hue and transitions into chronic edema occur among patients with onchocerca nodules (Robles after Fülleborn<sup>407</sup>). In both types of onchocerciasis the skin may become dry itchy infiltrated and coarsened (onchodermatitis). This pruriginous phase may look much like scabies<sup>408</sup> or neurodermatitis<sup>409</sup>. The microfilariae of *Onchocerca volvulus* can be found in the altered skin. Itching seems to be caused by allergic phenomena rather than by the active moving of the worms since heavily infected skin was found without associated pruritus<sup>410</sup>.

### Dracunculiasis or Dracontiasis (Guinea Worm)

The guinea worm (*Dracunculus medinensis* or *Fullebornius medinensis* formerly called *Filaria medinensis*) is in its larval stage a parasite of some microscopic crustacea of the genus cyclops which infects man though drinking water or through direct entrance into the skin. After one year the adult fertilized female which is one yard long and about as thick as a thread appears under the skin sometimes preceded by fever and urticaria<sup>411</sup>. A dome-shaped blister later an ulcer indicates its end. The lesion varies in diameter from 2 to 7 mm<sup>412</sup>. On

<sup>402</sup>Letkoitz M. and Mahleau. "Clinical Picture of Eosinophilic Disease With Eosinophilic Abscesses." *Harvard Bull.* 23: 122, 1941.

<sup>403</sup>Goldman L. "American Onchocerciasis." *Arch. Derm. & Syph.* 137: 245-290, 1941.

<sup>404</sup>Hoffman C. and Vargas L. "Cuerpos comunicacionales acerca de la onchocerciasis de Chiapas." *Rev. med. de Biol.* 13: 127-147, 1923. *Idem* 13: 785.

<sup>405</sup>Fülleborn P. "Ueber die Bedeutung der Onchocerciasis bei der deutschen Onchocerca-Fäure." *Arch. f. Schmerz.* "Neue eine Zusammenfassung über die auf Onchocerciasis bei den besprochenen Dermatosen und Versuche über den diagnostischen Wert der Analyse von mit Onchocerca-Antigen." *Arch. f. Dermat.* 1941. 104: 214-22, 1921.

<sup>406</sup>Anderson C. and Lebecher P. "Onchocerciasis (Guinea Worm) in Tunisia." *Arch. Int. Pathol.* 44: 103-112, 1940.

<sup>407</sup>Loewenthal L. J. A. "Onchocerciasis (Guinea Worm) in Chiapas." *Ann. Trop. Med.* 37: 147-148, 1942.

douching with cool water the worm will often protrude from a small hole and expell a fluid containing thousands of embryos.

The premonitory urticaria and pruritus and also asthma and diarrhea are probably caused by the same allergens in the excreta which cause the blister and ulcer. The microfilariae do not have the toxic or allergenic effect of the adult worm<sup>70</sup> which if injured or dead sometimes causes severe reactions. The therapy consists in cautious and patient extraction of the entire adult worm which takes about two weeks. This requires a certain technique which can be found in the textbooks on tropical diseases.<sup>71-74</sup>

### Cysticercosis

Normally the adult tapeworm (usually *Taenia solium*) is a parasite of the human ileum. Its eggs must get into the stomach of the swine where the hatched embryos travel to the points of encapsulation. Occasionally man is the intermediate host instead of the pig. Then he will harbor the encapsulated larvae most often in the brain and the eye only in 6 per cent of the cases in the subcutaneous tissues. The subcutaneous or cutaneous cysticerci are cysts of from one to several centimeters in diameter. They are round or oblong and are freely movable in the subcutaneous tissue. The cysts are of elastic hardness and non-tender numbering a few or several thousands. The inflammatory reaction is insignificant. If they are diagnosed they may help to explain other symptoms caused by cysticercosis of internal organs.<sup>75-78</sup> The prognosis of cysticercosis of the skin per se is favorable. The cysts usually stay without change and sometimes disappear spontaneously. The huge *echinococcus* cyst is the larva of a small tapeworm of the dog. The disease is very rare in the United States. An intracutaneous test with liquid from the cysts (Casoni test) and a complement fixation test are reliable.

The larvae of some tropical cestodes (*Sparganum proliferum*) may cause small acne like cutaneous cysts besides severe involvement<sup>79</sup> of almost the entire system in some of the few studied cases.<sup>80</sup>

### Bilharziasis

The adult worms of *Schistosoma hematobium* live in pairs in the portal system of man producing eggs which appear in the feces and in the urine. In water

<sup>70</sup>Fabry N H and Linton W G. Studies in Decapodiasis I. Indian J. M. Research 11: 915-932 1924.

<sup>71</sup>Fabry N H. Studies in Decapodiasis VI. Indian J. M. Res. 39: 439-454, 1924.

<sup>72</sup>Takamatsu H. Generalized Cysticercosis. Zentralbl. f. allg. Pa. h. u. path. Anat. 72: 2-3, 1929.

<sup>73</sup>Tasawara I and Repetz E. Ein Fall von Cysticercosis havis im Unterbauch des Menschen. Virchows Arch. f. path. Anat. 304: 555-558, 1930.

<sup>74</sup>Pick W. Tierische Parasiten der Haut. Handb. d. H. u. Ch. 9: 1 467-616 1929.

<sup>75</sup>Brinkford J F. Unrecognized Cysticercosis. Lancet 1: 137 139, 1942.

<sup>76</sup>Li C K, Go-Kai K. and Fraser C W. Subcutaneous Cysticercosis Cellulosa in Man. Five Cases. Arch. Derm. & Syph. 51: 777 780 1920.

<sup>77</sup>DeW. O W and Taylor L. The Larval Cestode (*Sparganum mansoni*) of Man Which May Possibly Occur in Returning American Troops. Bull. 33 Bureau of Animal Industry U. S. Dept. Agr. Washington, 1908.

they develop into larvae (cercariae) which are able to enter the human body through the skin.

Bilharziasis is predominantly a urinary disease. It is a public health problem of great importance in Egypt, Japan, China, and other countries, especially where work in flooded rice fields brings about the exposure to infection with cercariae.

**Dermadromes.**—The dermadromes are of little importance in comparison with the frequent and severe bladder involvement. The skin in the neighborhood of the urinary fistulae may contain huge numbers of often calcified eggs. The irritation from urine, pus, and infestation may give rise to *papillomas* of the anal and genital region which occasionally become malignant. Smderson<sup>197</sup> found in 20 per cent of the *schistosomiasis* (hematobium) cases that he observed in Iraq a sometimes reticulated, well-defined butterfly-shaped *hyperpigmentation* over the bridge of the nose and the cheeks. He believes that it is caused by a photosensitization of the skin under the influence of the worms (see under ancylostomiasis).

The entering cercariae of *schistosoma* hardly cause<sup>99</sup> dermatitis while the cercariae of otherwise innocuous trematodes have been held responsible for many epidemics of *swimmers itch*.

<sup>197</sup>Kinderson, H. C.: Anomaly of Pigmentation in Schistosomiasis, Tr. Roy. Soc. Trop. Med. 23: 633-634, 1930.

<sup>99</sup>Latz, A. and Latz, G. A.: Bilharziasis oder Schistosomiasis, Handb. d. path. Mikroorg. 8, 2: 873-906, 1929.

## CHAPTER X

### TUBERCULOSIS

The elementary facts concerning the tubercle bacillus and the general pathology of tuberculosis are so well known that it does not seem necessary to discuss them except for some phenomena which are of special importance in the pathogenesis of the cutaneous manifestations of internal tuberculosis.

If the skin of a *normal*<sup>706-711</sup> guinea pig is inoculated with tubercle bacilli the small wound heals primarily. After a week an inflammatory reaction sets in. A papule develops which during the third week forms an ulcer. There is little tendency to heal and some ulceration or infiltration usually still exists when the animal dies of generalized tuberculosis. During the second week lymphangitis and lymphadenitis are marked. The histological picture shows at first, an inflammatory reaction with many groups of tubercle bacilli. During the third week tuberculoid structures start to form and the number of bacilli decreases so that only occasionally can single rods be found. Tuberculin skin tests start to become positive about ten days after the infection. Within four weeks the entire skin has become sensitized.<sup>712</sup>

If the identical inoculation of tubercle bacilli is done in the skin of a guinea pig which at least four weeks *previously had been infected* with tuberculosis, an acute hemorrhagic edematous and sometimes necrotic reaction starts within twenty four hours reaches its height on the second day and then subsides rapidly. After about ten days a necrotic hemorrhagic crust is thrown off. After three to four weeks the lesion is usually healed. There is no additional lymphadenitis and no further ulceration. The histological examination reveals an acute inflammation. The scab which contains the bulk of the bacilli comes off the underlying erosion heals and is soon covered with normal epidermis. Sometimes tuberculoid structures are formed earlier than in the primary inoculation. It must be emphasized that this sequence of changes after primary and super infection known as *Koch's fundamental phenomenon* is subject to many variations and that great skill and experience are required to produce it in complete clarity. This is particularly true<sup>713</sup> of the experimental hematogenous i.e. intracardial infection of the guinea pig.

Two weeks after the intracardial injection of tubercle bacilli normal animals develop a papulo-squamous rash and die from generalized tuberculosis after four to five weeks. Tuberculous guinea pigs, however show during the second day a follicular rash which heals quickly after a latency of about two weeks.

<sup>706</sup>Lewandowsky F. Die Tuberkulose der Haut. Berlin, 916, Julius Springer.

<sup>707</sup>Reichberger M. B. and Wise F. Tuberculin. Newer Dermatological Considerations, Ciba, North America Ed. 1952, 931.

<sup>711</sup>Martenszka, R. Neue Ergebnisse auf dem Gebiet der Haut-überkennung. Die extrapulmonale Tuberkulose. Vienna, 1912, Urban and Schwarzenberg.

some papulocrustous lesions appear which heal spontaneously. The microscopic picture of the hematogenous lesion in the first infected animal is that of an inflammatory reaction of nonspecific character with abundant bacilli. The hematogenous lesions in superinfected animals are decidedly tubercular in structure consisting of epithelioid and typical giant cells. There is perivascular necrosis but hardly any bacilli can be detected. The lesions are often found in the follicular plexus<sup>70</sup>. Similar tuberculoid lesions can be produced by the intracardial injection of killed tubercle bacilli.

The interpretation of these experiments and many variations has been formulated by J. Jadassohn<sup>71</sup> and his pupils especially Lewandowsky in a rule which has been amply confirmed not only in tuberculosis but also in many other infections. This so-called *law of J. Jadassohn and Lewandowsky* states that unchecked growth of microbes causes nonspecific inflammation. Where however microbes are locally and not too rapidly destroyed by the immunobiologic defensive reaction tuberculoid structures develop. This law applies to the products of microorganisms.

Koch's fundamental phenomenon has been found valid in the human pathology. If the skin of a person who has not had tuberculosis before is infected with tubercle bacilli a lesion characterized by apud ulceration lymphangitis and lymphadenitis and abscess formation develops in the course of one to two weeks<sup>72-74</sup>. This syndrome which is best known from the cases of circumcision tuberculosis<sup>71, 75</sup> but also from other traumatic infections<sup>71, 76</sup> is called the primary complex of tuberculosis of the skin.

The number of bacilli in the ulcer is large so that they can be found in the direct smear. The tuberculin reaction is negative in the early stages but becomes positive three to eight weeks after the cutaneous infection (E. Löwenstein after E. H. Urbach<sup>75</sup>). The tuberculous primary complex of the skin is much rarer than its pulmonary counterpart the Ghon tubercle. Approximately one out of 750 cases of tuberculosis starts in the skin<sup>70, 77, 78</sup>.

Tubercle bacilli—for that matter also other microbes—spread very rapidly from a skin infection. Excision of a primary skin infection does not prevent

<sup>70</sup> For further pictures on experimental tuberculous see Sulzberger: *Dermatologic Surgery* 19.  
<sup>71</sup> Pictures of nodules prepared under the direction of Drs. G. Miescher and W. Jadassohn.

<sup>72</sup> Palsström H.: Post-traumatic Primary Tuberculous Infection of the Skin. *Acta der. Scandin.* 19: 246-259, 1932.

<sup>73</sup> Brunsward F.: So-called Primary Complex of Tuberculosis of the Skin. *Planta* 184: 248-249, 1932.

<sup>74</sup> Kohn W.: Der lokale Primärkomplex der Haut. *Skt. 39: 1*, 1932.

<sup>75</sup> Sichelmann H. P.: Primary complex of Tuberculosis of the Skin. *Review of the Literature*. *Arch. Dermat. & Syph.* 55: 549-551, 1915.

<sup>76</sup> O'Leary P. A. and Harrison M. W.: Inoculation Tuberculosis. *Arch. Dermat. & Syph.* 65: 371-390, 1941.

<sup>77</sup> Wolf E.: *Frey's Vermehrungsbefunde*. *Beit. Klin. Wochenschr.* 58: 1231, 1911.

<sup>78</sup> Pinkster L.: *Über die Heilungsmittel tuberculöser Hauterkrankungen*. *Praxis* 18: 123-124, 1932.

<sup>79</sup> Fisher H. H.: The Primary Cutaneous Tuberculous Complex. *J. A. M. A.* 100: 3021-3032, 1937.

<sup>80</sup> Schachermann G.: Primary Tuberculosis of Skin in Children. *Secondary Formation of Lupus*. *Arch. f. Kinderh.* 118: 31-32, 1939.

<sup>81</sup> Sichelmann H. E.: *Alters- und Resistenz in Tuberculosis*. *Journal-Lancet* 82: 230-231, 1915.

<sup>82</sup> Rank A. E.: *Angewandte Schriften zur Tuberkulosepathologie*. Berlin 1924, Julius Springer.

<sup>83</sup> Ghon A.: The Primary Complex of Human Tuberculosis. *Am. Rev. Tuberc.* 7: 314, 1922.

<sup>84</sup> Palsström H. A.: Primary Cutaneous Complex. *Inoculation Tuberculosis*. *J. Am. Med. Assoc.* 9.

systemic infection. Löwenstein was unable to prevent the generalization of a tuberculous infection from the hindleg of a guinea pig when he amputated the limb five minutes after the inoculation. A great number of similar observations have been made<sup>70</sup> showing that a truly local skin infection hardly exists. The primary tuberculous complex of the skin is of little practical, though of great theoretical importance. The majority of the tuberculous skin infections differ in two important points, from the primary complex. They occur in an already tuberculous and allergic organism and they are overwhelmingly autogenous and usually hematogenous. These two facts help to explain many of the characteristics of the tuberculodermas.

The great variety of clinical pictures of cutaneous tuberculosis is caused by the fact that neither the virulence of the tubercle bacilli nor the defense mechanisms of the human organism are powerful enough to bring about either a complete healing or a fatal course. The tuberculous infection can be compared to a war of position and attrition. J. Jadamohn believed that superinfection is the most important factor in developing lupus from a tuberculous infection. This has been widely accepted though some authors at least in some cases have placed more emphasis on the differences in the reactions of the infantile and adult human skins. Volk<sup>71</sup> sees an analogy in the difference of the primary tuberculous skin infection of the guinea pig which almost always develops an ulcerative and later generalized and fatal tuberculosis and the cutaneous infection of the rabbit in which the skin infection resembles lupus, remains localized and has a marked spontaneous healing tendency.<sup>72</sup>

The *bovis* type of the tubercle bacillus causes about 13 per cent of all cases of skin tuberculosis.<sup>73</sup> It has already been said that the *tuberculin skin test* becomes positive from three to eight weeks after the infection. The positive reaction is evidence of allergy against the tubercle bacillus and its products, but it does not indicate immunity or resistance. The complete breakdown of the resistance as encountered in miliary tuberculosis and cachexia may be accompanied by a breakdown of other systemic functions e.g. the ability to react with inflammation to the tubercle bacillus. In other words the tuberculin reaction may become negative. This phenomenon is called *negative energy*. However measles, influenza, and other infections, some forms of skin tuberculosis and especially the sarcoids<sup>74 75 76</sup> may prevent a positive reaction in an active

<sup>70</sup>The term *tuberculid* has been voided since it is confusing and unnecessary. It can be considered accepted that all tuberculids are tuberculosis (Sulzberger and Goodman,<sup>76</sup>) and that microorganisms are demonstrable in practically all tuberculids (Wise and Sulzberger<sup>76</sup>).

<sup>71</sup>Sulzberger M. B., and Goodman, J. Tuberculodermas, M. Clin. North America 36 904-1007 1936.

<sup>72</sup>Wise F. and Sulzberger M. B. Yearbook of Dermatology Chicago, 1932. The Yearbook Publishers, p. 373.

<sup>73</sup>Kadon, F. and Kallion-Deffner L. L. Ueber Allergie- und Immunitätsverhältnisse bei Hauttuberkulose. SK 68: 273-348, 1932.

<sup>74</sup>Diets, J. Ueber die Typen der Tuberkelbacillen (TB) bei Hauttuberkulose. Arch. f. Dermat. Syph. 179: 380-388, 1939.

<sup>75</sup>Zieler and Häsel. Hauttuberkulose in ihren Beziehungen zur Tuberkulose innerer Organe. Ergebn. d. ges. Tuberk. Forsch. 6 428, 1934.

<sup>76</sup>Flaner M. Non-Cahecting Tuberculosis. Am. Rev. Tuberc. 37 690, 1936.

way by production of inhibiting substances which are called anticutins.<sup>724</sup> This is called *positive energy*. In such cases the resistance to infection e.g. with the bacillus Calmette-Guérin may be very high.<sup>725</sup> The conception of positive energy is based on the noncachectic cases with positive tuberculosis and one of the mentioned conditions especially the sarcoids, in which the tuberculin reaction is negative.<sup>726</sup>

The methods of skin testing for tuberculin allergy are the same as those used in testing other kinds of allergic conditions.

1. The intracutaneous injection.<sup>728</sup> This test is very accurate in J. Jadassohn's graded quantitative method which consists of the simultaneous intradermal injections of 0.1 c.c. of dilutions of old tuberculin—Koch (OTK) in concentrations of 1:1 000 000 1:100 000 1:10 000 and in some cases 1:100 and 1:10 and control saline wheals.<sup>729</sup> More often purified protein derivative (PPD) is used. This is available in convenient tablets of two strengths which have to be dissolved in 1 c.c. of diluent. One-tenth cubic centimeter of fresh first strength solution (0.0005 mg) is injected first. If no reaction within 48 hours occurs 0.1 c.c. of fresh second strength solution (0.005 mg) is injected into the other arm.

2. The scratch or abrasion test (von Pirquet)<sup>730</sup> with OTK.

3. Theunction of a 50 per cent tuberculin lanolin salve.<sup>731</sup>

4. The patch test.<sup>732</sup>

For the technique of these tests, the reader is referred to textbooks of allergy and tuberculosis for comparative evaluation to E. Friedman, M. H. Black and A. L. Ewerman, M. Salsberger and F. Wae.<sup>33</sup>

The patch test is a convenient and sufficiently reliable method for preliminary information. Urbach<sup>34</sup> advises following up a patch test which is negative after one week with the more sensitive Mendel-Mantoux test. In all tests the reaction can be considered positive if an inflammatory papule of at least 5 mm in diameter develops. The papule reaches its height in forty-eight to seventy-two hours and then slowly fades. Immediate reactions are not specific.

<sup>724</sup>Kawai, F. Mantuberculose. Ter Spravy 6: 137-186. from Zusammenfassung 190-197 1934 Zbl. 69: 504

<sup>725</sup>Pinner, M. Wynn, M. and Cohen, A. C. Procritis and Anticritin, Yale J. Biol. & Med. 18: 450-463, 1943

<sup>726</sup>Martenssen, H. and Voss, B. Statistische Untersuchungen über die Tuberculin Reaction, Arch. f. Derm. Syph. 188: 400-1939

<sup>727</sup>Lowy, H. Saeck. Sarcoid and Lupus Pernio. Dissertation, Breslau 1921

<sup>728</sup>Mendel, F. Die Pirquet'sche Hautreaktion und die intracutane Tuberculinbehandlung, sk. Med. Klin. 4: 403-404, 1909

<sup>729</sup>Man, O. C. Intracutaneo-Tuberculin Reaction, München med. Wchnschr. 55: 2117, 1909

<sup>730</sup>Von Pirquet, C. Tuberculin-Diagnose durch cutane Impfung, Berl. klin. Wchnschr. 46: 644, 1907

<sup>731</sup>More, E. Ueber eine diagnostisch verwertbare Reaction der Haut auf Einspritzung mit Tuberculin, München med. Wchnschr. 55: 216, 1909

<sup>732</sup>Nathan, E. and Kados, F. Ueber eine epidermale Tuberculinreaktion bei Mantuberculose, Zbl. Wchnschr. 1931 II: 2392-2393

<sup>733</sup>Volzner, H. and Goldberger, E. W. A New Tuberculin Patch Test, Am. J. Dis. Child. 53: 1019, 1937

<sup>734</sup>Friedman, E. Black, M. H., and Ewerman, A. L. Tuberculin Tests, Am. J. Dis. Child. 46: 45-65, 1933.

A *positive reaction* in children under seven years is generally a sign of active tuberculosis. Beyond seven years the positive test must be correlated with the clinical picture. In adults a positive test does not prove more than the well known fact that almost everybody once in his life becomes infected with tuberculosis. In the vast majority of the cases the disease becomes arrested after the primary stage leaving behind an allergy to tuberculin.

A *negative tuberculin test* especially the Mendel Mantoux test must with the mentioned exceptions, be interpreted as indicative of the absence of a tuberculous infection of more than 8 weeks.

### Hematogenous Skin Tuberculosis

Skin tuberculosis may develop by ectogenous inoculation into the skin and by endogenous infection. The tuberculosis verrucosa cutis of the hands in slaughterhouse workers the postmortem wart and the lupus of the buttocks in small children who sit on the floor of a tubercle bacilli-infected room are examples of ectogenous tuberculous skin infection. The endogenous infection of the skin plays a more important part. Endogenous lupus by contiguity from underlying tuberculous lymph nodes especially of the neck is a common occurrence in countries where skin tuberculosis is more frequent than in America. The lymphogenous spread of lupus is known. However compared with these ways of infection the hematogenous tuberculous infection of the skin is far more important. Foci of tuberculous infection which are capable of releasing tubercle bacilli into the bloodstream are very common. Even old calcified lymph nodes may still contain virulent tubercle bacilli as has been shown in autopsies of patients who for many years suffered from hematogenous crops of lupus. It is more difficult to explain why there is so little hematogenous skin tuberculosis in view of the frequency of the foci and of the bacilli in the blood than it is to give reasons for the hematogenous nature of many cases of cutaneous tuberculosis. It can be considered a fact that more than 50 per cent of the lupus cases are caused by hematogenous infection<sup>72</sup> mostly from pulmonary or lymphatic foci.<sup>73</sup>

The relationship of pulmonary tuberculosis to cutaneous tuberculosis has been the subject of many investigations. Pulmonary tuberculosis has been found existing simultaneously with skin tuberculosis, especially lupus vulgaris in percentages differing as widely as 8 and 90 per cent. An analysis of 300 lupus cases in Münster Germany<sup>74</sup> showed 12 per cent more or less active and 60 per cent inactive pulmonary tuberculosis while in a control group of about 5000 German university students only 1 per cent active and 18 per cent inactive lung cases could be found. St. Epstein<sup>75</sup> determined 16 per cent as the incidence of active pulmonary tuberculosis in 200 lupus patients. In 429 fatal lupus cases visceral usually pulmonary tuberculosis was the cause of death in

<sup>72</sup>Kremer E. Untersuchungen über Haut tuberculosis Wienburg Abh Bd 37 H 2, 1931

<sup>73</sup>Rasmussen J E. Tuberculosis of the Skin, Arch. Dermat. & Syph 23 399-406 1934.

<sup>74</sup>Wilsen G. W. Untersuchungen bei 300 Lupuskranken, Zeitschr. f. Tuberk. 79 84-88, 1934.

<sup>75</sup>Epstein, St. Tuberculosis of Lungs in Patients With Sarcoidosis, Granuloma Annulare and Lupus Erythematosus, Arch. Dermat. & Syph 42: 10, 1940



48 per cent.<sup>744</sup> From these and many other statistics it can be concluded that the incidence of lung tuberculosis in lupus is a high one. On the other hand the percentages of skin tuberculosis in very large groups of tuberculous patients has always been found low 0.2 per cent<sup>747</sup> 1 per cent in 27,540 cases<sup>74</sup> less than 2 per cent in 18 000 cases<sup>749</sup>. This compares well with many older statistics<sup>750</sup> and seems to bear out the old rule that lupus patients often become consumptive *but that consumptives rarely develop lupus*. While the figures seem to be very low the incidence of skin tuberculosis is still about 2 to 3 times higher in patients with pulmonary tuberculosis than in a comparable normal group. Similar tendencies as in the relationship of lupus and pulmonary disease prevail in its relation to surgical tuberculosis. Among 275 lupus cases were 16 per cent with bone or joint tuberculosis while among 371 cases with tuberculosis of the bones and joints only 5 per cent had lupus.<sup>744</sup> The isolation of tubercle bacilli from the blood either by animal inoculation or by culture with the Löwenstein method has recently been more often successful than was held possible before. It is true that many observers could not obtain the same results as Löwenstein.<sup>751</sup> The positive findings however carry more weight than the negative ones. Kren<sup>58</sup> could show that if blood culture of patients with lupus vulgaris erythema induratum and lupus erythematosus was done more than seven times positive cultures could be found in all cases. The frequently negative blood cultures are most likely due to technical difficulties to unfavorable time of testing and to the too small numbers of the investigations. In Kren's<sup>58</sup> series the blood specimens up to nineteen different ones from one patient were sent to Löwenstein without diagnosis. It is believed that the irregularity of the showers of bacilli appearing in the blood is responsible for the inconstant findings. However with or without confirmation<sup>752</sup> of all of Löwenstein's findings the frequent occurrence of tubercle bacilli in the blood of patients with skin tuberculosis is a fact.<sup>38-39-419 753-755</sup>

<sup>744</sup>Stenopols, G. Skin Tuberculosis, Causes of Death. Arch. f. Dermat. & Syph. 223 216-222, 1942.

<sup>745</sup>Griesbach, R. Hautkrankheiten bei der Lungentuberkulose mit besonderer Berücksichtigung der Alvea. Kocher's Tuberk. 67: 404-416 1930.

<sup>746</sup>Baia, S. J. Skin Disease in Pulmonary Tuberculosis, Dermatologia 66 17-18, 1943.

<sup>747</sup>Gall, O. Clinical Types of Pulmonary Tuberculosis Associated With Skin Tuberculosis, Tuberkulose 1 243-249 275-279 [Hungarian with German summary; Ed. 67 242].

<sup>748</sup>Jeyer, J. Tuberculosis als Organismenkrankung, Acta tuberc. Scandin. 6: 67-222, 1935 Ed. 68 209.

<sup>749</sup>Kelle, W. and Küster, E. Tuberkelbacillen im strömenden Blute, Deutsche med. Wchnschr. 1934 I 300-313.

<sup>750</sup>Rabin, E. H. Heterogeneous Tuberculosis in Adult Generalized Homogeneous Tuberculosis, Am. Rev. Tuberc. 59: 557-565 1939.

<sup>751</sup>Wilson, O. S. Tuberculosis Bacillæmia, Medical Research Council, Special Report Series, N 122, London, 1933.

<sup>752</sup>Stalkiewicz, A. F. Resultat mit der Löwensteinischen Bakterienmethode bei verschiedenen Formen der Hauttuberkulose, Wien. klin. Wchnschr. 45 719-720 1932.

<sup>753</sup>Illich, T. Löschung von Tuberkelbacillen aus strömendem Blut, Schweiz. med. Wchnschr. 1933 I 307-310.

<sup>754</sup>Popper, H. Bodart, F. and Schindler, W. Tuberkelbacillenzüchtung aus dem Blut II Virchows Arch. f. path. Anat. 236 618-627 1932.

<sup>755</sup>Courment, P. Gais, J. and Michel, H. J. Bacillæmia hereditaria et tuberculosis cutanea, Presse méd. 42 497-499 1934.

<sup>756</sup>Ora, A. Sul valore del metodo Löwenstein per lo studio della bacillæmia, nella tubercolosi cutanea, Atti (abstr.) Arch. Ital. di dermat. 38 3-18, 1937.

<sup>757</sup>Löwenstein, E. Tuberculous Bacillæmia and Its Significance in Medicine Quart. Bull. Health Organ. League of Nations 4 219-232 1935.

The start of cutaneous tuberculosis in the intima of veins was demonstrated a long time ago<sup>33</sup> The distribution of the lesions in the cases of post-exanthematic lupus<sup>34</sup> hardly allows any other explanation than general spread by the circulation with selective take in some sites and failure to take in others (see chapter on hematogenous skin infection)

Blood borne infection may lead to all of the well-known pictures of skin tuberculosis. While hematogenous infection is the cause of the papulonecrotic and indurative types of tuberculosis and of the majority of the lupus vulgaris cases, it is much less common in scrofuloderma and only few instances have become known in tuberculosis verrucosa cutis.

### Cutaneous Tuberculosis

The primary lesion of *lupus vulgaris* regardless whether of endogenous or ectogenous origin is the *lupus nodule* as it is called though it is usually only a *macule*. In its early and uncomplicated stage this is a pinhead to lentil-sized red or copper-colored smooth spot. Under glass pressure the spot does not fade and the blanching of the surrounding skin makes it stand out more clearly in a red brownish or dark yellow color. In suitable light it is strikingly trans-

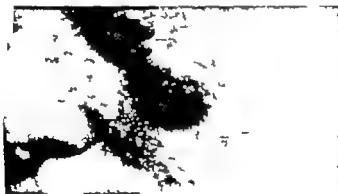


Fig. 94 — *Lupus vulgaris* (nodules). Courtesy Dr. M. Jemner.

parent which is responsible for the often used comparison with apple butter. If one gently tries to penetrate the surface with a fine bulbous probe one is surprised how easily the instrument sinks into the soft tissue at a degree of pressure which would not be sufficient to pierce normal skin. Such early lupus nodules are most commonly seen on the face particularly on and around the nose. The great variety of pictures which may be encountered during the course of lupus vulgaris can be explained by a number of factors the dominant role of any one being able to create a clinical variety. Increase in number and coalescence of the spots may lead to extremely chronic patches of flat lupus which may be as small as pea or cover entire regions. Such large flat lesions

<sup>33</sup>Artoon, M. Tuberculous cutaneous post-morbillose. Arch. Ital. di dermat. 8 232-233 1923

48 per cent.<sup>72</sup> From these and many other statistics it can be concluded that the incidence of lung tuberculosis in lupus is a high one. On the other hand the percentages of skin tuberculosis in very large groups of tuberculous patients has always been found low 0.2 per cent<sup>73</sup> 1 per cent in 27,540 cases<sup>74</sup> less than 2 per cent in 18 000 cases.<sup>75</sup> This compares well with many older statistics<sup>76</sup> and seems to bear out the old rule that lupus patients often become consumptive but that consumptives rarely develop lupus. While the figures seem to be very low the incidence of skin tuberculosis is still about 2 to 3 times higher in patients with pulmonary tuberculosis than in a comparable normal group. Similar tendencies as in the relationship of lupus and pulmonary disease prevail in its relation to surgical tuberculosis. Among 275 lupus cases were 16 per cent with bone or joint tuberculosis, while among 371 cases with tuberculosis of the bones and joints only 5 per cent had lupus.<sup>77</sup> The isolation of tubercle bacilli from the blood either by animal inoculation or by culture with the Löwenstein method has recently been more often successful than was held possible before. It is true that many observers could not obtain the same results as Löwenstein.<sup>78</sup> The positive findings however carry more weight than the negative ones. Kren<sup>25</sup> could show that if blood culture of patients with lupus vulgaris erythema induratum and lupus erythematosus was done more than seven times positive cultures could be found in all cases. The frequently negative blood cultures are most likely due to technical difficulties to unfavorable time of testing and to the too small numbers of the investigations. In Kren's<sup>25</sup> series the blood specimens, up to nineteen different ones from one patient were sent to Löwenstein without diagnosis. It is believed that the irregularity of the showers of bacilli appearing in the blood is responsible for the inconstant findings. However with or without confirmation<sup>79</sup> of all of Löwenstein's findings, the frequent occurrence of tubercle bacilli in the blood of patients with skin tuberculosis is a fact.<sup>25,30,41,72-75</sup>

<sup>72</sup>Szencsik, E. Skin Tuberculosis, Causes of Death. Arch. f. Dermat. & Syph. 163 215-222 1942.

<sup>73</sup>Griesbach, R. Hautkrankheiten bei der Lungentuberkulose mit besonderer Berücksichtigung der Akne. Ztschr. f. Tuberk. 57 406-416 1930.

<sup>74</sup>Reisató J. Skin Disease in Pulmonary Tuberculosis. Dermatologica 68 17-41, 1943.

<sup>75</sup>Ogil, G. Clinical Types of Pulmonary Tuberculosis Associated With Skin Tuberculosis. Tuberkulose 1 253-259 373-379 (Hungarian) (in German summary) Zbl. 67 342.

<sup>76</sup>Jøyer J. Tuberkulose als Organisationskrankung. Acta tuberc. Scand. 9 67 233, 1935; Zbl. 55 809.

<sup>77</sup>Hoße W. and Küster E. Tuberkulobacillen im strömenden Blute. Deutsche med. Wchnschr. 1934 I 300-313.

<sup>78</sup>Klein, E. H. Hematogenous Tuberculosis in Adult. Generalized Hematogenous Tuberculosis. Am. Rev. Tuberc. 28 557-584 639.

<sup>79</sup>Wood, O. S. Tuberculous Bacillæmia, Medical Research Council, Special Report Series, No. 163, London, 1933.

<sup>80</sup>J. Kren, A. F. Resultat mit der Löwenstein'schen Blutkulturmethode bei verschiedenen Formen der Hauttuberkulose. Wchnschr. 48 719-720 1923.

<sup>81</sup>Illich, T. Züchtung von Tuberkulobacillen aus strömendem Blute. Schweiz. med. Wchnschr. 1933 I 307-310.

<sup>82</sup>Popper H. Badart, F. and Schindler W. Tuberkulobacillensichtung aus dem Blute II. Virchows Arch. f. path. Anat. 296 618-637 1933.

<sup>83</sup>Courmont, F. Gafé J. and Michel, F. J. Bacillémie tuberculeuse et tuberculose cutanée. Presse méd. 42 487-493, 1934.

<sup>84</sup>Oro, A. Sul valore del metodo Löwenstein per lo studio della bacillæmia, nelle tubercolosi cutanee. Arch. Ital. di dermat. 12 3-16, 1937.

<sup>85</sup>Löwenstein, E. Tuberculous Bacillæmia and Its Significance in Medicine. Quart. Bull. Health Organ., League of Nations 4 319-322, 1935.

Fig. 97



Fig. 98

Fig. 97.—Lupus vulgaris surrounding the ear lobe. Exceedingly chronic course; note worn-off ear lobe.

Fig. 98.—Lupus vulgaris. A small lesion had been excised and the defect covered by full-thickness transplantation. Recurrent lupus lesions still in invade the transplant. Yellowish lesions.

are often scaly so that they may resemble psoriasis; this is still more likely if the outlines are circinate. The tuberculous tissue may grow above the skin level and form elevated hypertrophic and even fungating or tumorlike granulations. *Lupus hypertrophicus*, *lupus tumidus* and other terms describe this variety which usually involves the nose, the lips and the lobe of the ear.



FIG. 99.—*Lupus vulgaris*. (Courtesy Dr. M. J. J. J. J.)

*Ulceration* and crust formation are more often a feature of the hypertrophic than of the flat forms. In the latter the ulceration is usually shallow and more marked along the edges. The healing tendency and scar formation vary though healing is rarely complete. The lupus may spread with an active *serpiginous* edge over large areas leaving in its wake a scar which usually contains some lupus nodules. Such annular or gyrate lesions may resemble syphilis or ringworm. The face may gradually become scarred, shrunken and immovable, and the conjunctiva and finally the eye itself may be destroyed. The mouth may be reduced to a small rigid hole. Such terminal stages may equal leprosy in dreadfulness. Cancer is not an uncommon complication. The suffering of such patients is beyond description. Such cases are fortunately rare especially in America but they can be seen in numbers in all the European lupus hospital. This tragic outcome however is an exception. In the vast majority of the cases the lesions are stationary or slowly progressive and often

amenable to treatment. Recurrences are very common. Spontaneous regression occurs but is rarely complete.

The *histology* of the lupus nodule shows a conglomeration of typical tubercles with epithelioid cells, giant cells, lymphocytes and central necrosis, the latter often not particularly marked. The same factors which by their dominance decide the clinical picture also produce a great histological variety.



FIG. 100. *Lupus vulgaris*. (Courtesy Dr. Garrett Cooper.)

It is now almost generally accepted that *lupus* is the expression of a cutaneous tuberculous superinfection with own or other tubercle bacilli. Existing tuberculosis shapes a tuberculous infection of the skin into lupus, thus making it a manifestation of an internal disease. *Lupus vulgaris* starts in 53 per cent of the cases during the first two decades of life<sup>70</sup> a fact which is not easy to explain. Scrofuloderma and children's diseases like measles may play a part though convincing cases are not very common. the postexanthematic lupus is a good example of hematogenous lupus<sup>70</sup>. It is not too rarely seen to start shortly after or even during the measles and also after other acute exanthema. The postexanthematic lupus is often disseminated and appears simultaneously in several or many spots. Artom<sup>70</sup> suggests that the anergy during measles favors the development of postexanthematic lupus. The prognosis is relatively good since the seeded lesions usually remain inactive<sup>70</sup>.

<sup>70</sup>Zieler, K. Primary Appearance of Chronic Skin Disease at Various Ages, with Special Reference to Lupous Tuberculosis. *Arch. f. Dermat.* Syph. 103: 297-302, 1942.

<sup>71</sup>Leisner, O. and Spiller, F. Cober disseminierter Hauttuberkulosen im Kindesalter. *Ergebn. d. inn. Med.* 7: 1911.

*Lupus miliaris disseminatus* (*Lupus follicularis* Tilbury Fox 1878) is a follicular form of lupus which almost always affects the face only. It has a great similarity to acne and rosacea. In fact most cases go under these diagnoses for a long time. After an initial stage of erythema has passed follicular papules develop often with scales a yellow center erythema and subcutaneous nodules. The lesions are distributed over the nose the cheeks the chin and though less pronounced the forehead and other parts of the body. On close diascopic inspection the apparently pustular efflorescences show typical lupus tissue. The lesions appear in crops do not coalesce do not contain pus and have a marked healing tendency. The histological picture is that of typical tuberculosis. The distribution in the perifollicular vascular plexus and other histological findings prove the hematogenous character. Tubercle bacilli have rarely been found in the lesions. Pulmonary and other visceral tuberculosis has been found in a considerable number of the cases but the tuberculin reaction is often weak. The prognosis of the condition itself<sup>70</sup> is favorable and it responds well to peeling with strong ultraviolet light.

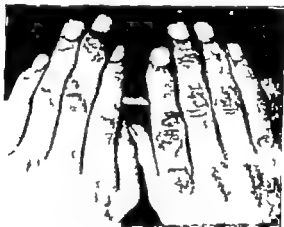


Fig. 101. Tuberculosis verrucosa cutis. Courtesy (the late Dr. W. A. Peery from Patton and Patton, Diseases of the Skin, The C. V. Mosby Company.)

*Tuberculosis verrucosa cutis* starts as a firm prominent nodule differing from lupus by the lack of transparency and the great resistance to the piercing probe. The papules increase peripherally coalesce but little become hyperkeratotic and later verrucous. Follicular abscesses are common especially in lesions which have reached more than coin size and greater thickness. The patches may reach great size. They are frequently seen over the bony prominences of the hands and feet. The right hand is most often affected<sup>71</sup>. The knuckles and the ankle areas are affected only occasionally. The lesions are mostly single or few in number but hematogenous dissemination with many

<sup>70</sup>Peck, A. M. *Lupus Miliaris disseminatus as faried*, Arch. f. Dermat. u. Syph. 188: 845-855, 1929.

<sup>71</sup>Lederhans, K. H. Statistische Untersuchungen über Tuberculosis verrucosa cutis, Arch. f. Dermat. Syph. 167: 163-164, 1932.

lesions has been seen. There is a decided preponderance of the male sex because the disease is often an occupational infection of slaughterhouse workers who are usually males but occasionally the disease also occurs in other persons who have contact with tuberculous material. The occupational character accounts for the common distribution on the hands and feet. It also occurs as an autogenous



Fig 102.—Scrofuloderma. (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)

superinfection with the sputum of patients with pulmonary tuberculosis. The bovine type of the tubercle bacillus has been found in 50 per cent or more of the cases, and bovine infection is probably responsible in all slaughterhouse cases.

Volk states that no explanation could be given why in one case tuberculosis verrucosa and in other cases lupus results from superinfection. Probably in spite of exceptions, the terrain of the hands and feet which has a greater keratotic tendency than other parts is one of the influencing factors. This is illustrated



by cases of hematogenously disseminated skin tuberculosis with tuberculosis cutis verrucosa on the arms and lupus on the face.<sup>300 723</sup>

The close similarity of tuberculosis verrucosa cutis and some phases of blastomycosis must be emphasized. Verrucous tuberculosis has a greater tendency to heal than lupus vulgaris and the response to treatment is more complete. The microscopic picture is that of tuberculosis but combined with parakeratosis and hyperkeratosis. Lymphangitis is a frequent complication.



FIG. 103. Tuberculosis cutis colliquativa (scrofuloderma). (Courtesy Dr. M. Jensen.)

*Tuberculosis colliquativa (scrofuloderma)* is a cold abscess of the skin most frequently originating in a subcutaneous tuberculous focus usually a lymph node or bone. It starts as a subcutaneous nodule which becomes adherent to the skin and forms an abscess or sinus without acute symptoms. Several such lesions may coalesce into a network of sinus abscesses scars and ulcers not infrequently surrounded by lupus. The most common site of scrofuloderma is the neck with its great number of easily infected lymphatic nodes. Tuberculosis of the sternum and of the ribs are other starting points for colliquative tuberculosis of the skin. Children and young adults are most often affected. Scrofuloderma occurs occasionally mostly in young children in a hematogenous

distribution without connection with underlying structures. These cases closely resemble the corresponding phases of sporotrichosis, blastomycosis and coccidioidomycosis. The prognosis of scrofuloderma and the therapeutic response is usually good though the process may last several years.

*Ulcerative tuberculosis of the orifices* in pulmonary or genitourinary tuberculosis produces characteristic lesions most often found on the tongue and around the anus but also on the lips, the ears and the glans penis. On the tongue the lesions may appear as shallow, jagged, oblong round or rhagadiform ulcers, the papular primary stage of which is seldom seen. The floor of the ulcer is granulated and yellowish, the edge slightly undermined. The lesion progresses by a coalescence with minute pustular lesions in the surroundings. There is little induration and sometimes surprisingly little, sometimes surprisingly severe pain. Perianal ulcerative tuberculosis occurs in 5 to 10 per cent of patients with pulmonary tuberculosis. All abscesses and fistulae in such patients must be considered suspects.<sup>765-769</sup>



FIG. 101.—Tuberculous ulcer of the tongue in pulmonary tuberculosis.

This ulcerative type of lesion contains more tubercle bacilli than the other forms. In line with this fact is the frequent absence of typical tubercular structures and the dominance of nonspecific inflammation. Ulcerative tuberculosis of the tongue is more frequently seen in men than in women.

Tuberculous ulcers of the orifices are important indicators of visceral, especially pulmonary, tuberculosis.<sup>767-769</sup>

<sup>765</sup>Garnes, E. and Greenaway, J. Perianal Tuberculosis. *Quart. J. Med.* New Ser. 11: 441-452, 1939.

<sup>766</sup>Shelley, R. M. *Internal Medicine Clin. North America* 17: 79-201, 1927.

<sup>767</sup>de Arco, H. and Miller, J. W. Tuberculosis of the Tongue. *Report of Three Cases*. *J. A. M. A.* 97: 108, 1930.

<sup>768</sup>Nicola, J. and Michel, P. *Infra-linguothoracique d'ulcère de la langue*. *Rev. franc. de dermat. et syph.* 27: 5-477, 1930.

<sup>769</sup>Wiel, P. *Der. urol.* 1930. *La rinoscopia della tubercolosi herosa della cav. delle narici*. *Dermatologica* 7: 279-4, 1927.

While the forms of cutaneous tuberculosis so far mentioned start predominantly from single lesions the following varieties have in common an

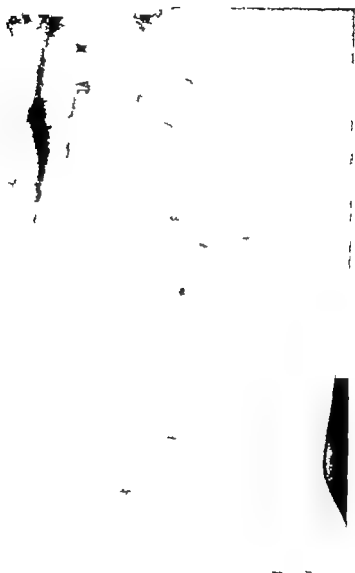


FIG. 103. *Lichen scrofulaceus* (= *tuberculosis lichenoides*) in a patient. (Courtesy H. M. Jansen)

*exanthematic* though not always copious distribution. Number and distribution have more importance than the features of the individual lesions which are usually small and not destructive.

*Miliary tuberculosis* of the skin is almost exclusively seen in infants and young children.<sup>77, 78</sup> In adults the miliary foci are numerous in the subcutis but do not reach the skin. The rash consists of pinhead sized, hardly prominent, often hemorrhagic and slightly umbilicated papules. These lesions are quite dense in some areas. They may heal spontaneously leaving a slightly depressed pigmented spot. The exanthem is inconspicuous and may easily be overlooked.<sup>79</sup> The diagnosis is rarely made without biopsy. The histologic structure is not so much tuberculoid as inflammatory in character. There are tremendous numbers of bacilli. Small vessels are sometimes solidly packed with bacillary emboli<sup>79</sup> and surrounded by necrosis, but there is a vast disproportion between the number of bacilli and tissue defense.<sup>78</sup> The tuberculin reaction is sometimes negative.<sup>78</sup> Hoyle and Valzey<sup>74</sup> list about 16 per cent tuberculous skin manifestations in their series of 120 cases of miliary tuberculosis. The prognosis is hopeless.



Fig. 66.—*Lichen scrofulosorum*. (Courtesy Dr. Erich Urbach.)

In *tuberculosis lichenoides* or *lichen scrofulosorum* large numbers of micropapular, mostly follicular, often conical and keratotic, skin-colored or pink to yellowish brown lesions are grouped in round, oblong or irregular patches. They are mostly found on the back, particularly in the lumbosacral region and on the abdomen. The lesions develop slowly and patches may persist for years. Older lesions often have a scale and if they are packed very closely together in old plaques, a large desquamating surface may give a

<sup>77</sup>Gutpat F. Die Beteiligung der Haut bei Miliartuberkulose. *Virchow Arch. f. path. Anat.* 226: 561-602, 1932.

<sup>78</sup>Koch H. Die Tuberkulose des Säuglingsalters. *Erkrank. d. inn. Med. u. Kinderh.* 11: 79-91, 1915.

<sup>79</sup>Wells R. Hansen's acute multiple subcutaneous tuberculous abscesses. *Ann.* 41: 479.

<sup>80</sup>Medelmann E. Tuberculosis cutis miliaris acuta generalisata im Kindesalter. *Jahrb. f. Kinderh.* 131: 34-35, 1931.

<sup>81</sup>Hoyle and Valzey. *Acute Miliary Tuberculosis*. London, 1937. Oxford University Press.

psoriasiform appearance. Usually the center of such plaques is less scaly than the edges but more grater or chagreen leather like. In some cases some or all of the papules bear a hard sharp horny little spine. The microscopic picture shows almost invariably tuberculoid structures without or with very few bacilli.



FIG. 107. Papulonecrotic tubercle. (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)

Phlyctenular conjunctivitis is a frequent accompaniment. The dermatosis is of great symptomatic significance. It indicates, almost always the existence of internal tuberculosis, usually of a more benign type. The dermatome is rare in adults more common in children. It frequently makes its appearance after measles and other acute infections. However there are great geographic differences. Tuberculosis cutis lichenoides is a common sight in the European skin clinics while in North America and particularly in the tropics and subtropics it is like all types of skin tuberculosis either rare or nonexistent<sup>10</sup> (Pusey after Volk<sup>10</sup>)

*Tuberculosis papulonecrotica* This variety of cutaneous hematogenous tuberculosis has been described under a score of names<sup>11</sup> among which the odd terms follicitis and acnitis are still being used because they were given by the first describer T Barthélemy. The term tuberculid is also often applied.

The evolution of the lesion is simple and characteristic. A cutaneous nodule of linseed size grows within about four weeks to its maximal size which does not exceed that of a cherry stone and becomes a movable firm well defined slightly raised dusky bluish red or brown papule. The center of the fully developed papule shows a yellow head which however does not contain pus as one might expect, but a rather tough necrotic core which may come out by itself leaving a small punched-out ulcer. More often a deep necrotic scab is formed which comes off after two to four weeks, producing a small crater shaped scar with sharp steep pigmented edges. The scars are often more characteristic than the active lesions. Papulonecrotic tuberculosis is usually fairly evenly disseminated over the arms hands, and legs, and occasionally the trunk. The extensor surfaces the skin about the joints and the buttocks are more often affected but no area is immune.

Genital lesions may suggest secondary syphilis.<sup>12</sup> Barthélemy called acnitis a deeper situated acneiform papulonecrotic tuberculosis of the face. This condition is closely related to lupus miliaris faciei. The lesions of papulonecrotic tuberculosis appear in crops and have a much more marked spontaneous healing tendency than other forms of skin tuberculosis. This type of skin tuberculosis is less responsive to tuberculin than is lupus.<sup>13</sup> The macroscopic structure is tuberculoid. Tubercle bacilli are scarce but have quite often been found particularly in children.<sup>14</sup>

Combination with pulmonary and other forms of tuberculosis including skin tuberculosis is the rule.

*Tuberculosis indurata* (Erythema induratum Bazin's disease) is a rather rare dermatosis characterized by cutaneous or subcutaneous nodules or plaques of much larger size than in the papulonecrotic lesions. There are usually only a few lesions scattered over both legs especially the calves and rarely also over the posterior aspects of the thighs the buttocks, the forearms or the face. They start as indolent nodules, which grow within several weeks, to almond or even

<sup>10</sup> Also E. Incidence of Tuberculosis of the Skin, Arch. Dermat. & Syph. 48 120-124, 1942.  
<sup>11</sup> Barthélemy A. H. L. Acnitis de T. Barthélemy, Arch. dermat.-syph. Hôp. St. Louis 8 272-276 1917.  
<sup>12</sup> Trichard Papular Papulonecrotic Tuberculid I Negro, Arch. Dermat. & Syph. 47 827 828, 1942.

palm size. Such fully developed lesions are visible as a pink or lavender smooth erythema resembling the lilac ring of scleroderma. Palpation reveals an indurated plaque of varying depth which is sometimes connected with cordlike phlebitic changes. The infiltrate is movable with the skin and usually is not tender. In larger lesions the center is depressed or it may though rarely become ulcerated and then resemble a syphilitic gumma. The plaques heal upon



Fig. 108



Fig. 109

Fig. 108 Tuberculosis indurata (erythema induratum) (Courtesy Dr. M. Jensen)

Fig. 109 Tuberculosis indurata (erythema induratum) (Courtesy Dr. M. Jensen)

taneously but the course may take many weeks, months, or even years if ulceration occurs. The oral mucosa is occasionally involved.<sup>77, 78</sup> The dermatome is many times more common in the female than in the male sex. New crops are usually observed during the winter and spring.<sup>79</sup> The tuberculin reaction is strongly positive. Tubercle bacilli are rarely found in the lesions. The struc-

<sup>77</sup>Achickiacki, J. Erythema induratum, *m. Arch. f. Dermat. & Syph.* 90: 371, 1904.

<sup>78</sup>Farmer, A. Erythema induratum, *Arch. f. Dermat. & Syph.* 103: 90, 1927.

ture is decidedly tubercloid. Combination with visceral tuberculosis and with other forms of cutaneous tuberculosis is not rare.<sup>200</sup>

**Rosacea-like Tuberculosis** Lewandowsky<sup>201</sup> described this form of skin tuberculosis which in the majority of cases is seen in women<sup>202 203 204</sup> of 30 to 60 years of age. The disorder develops gradually. The typical case shows a great number of papules, mostly follicular scattered symmetrically over the cheeks and forehead often leaving the nose and chin free. The papules are small to medium sized with a decided yellowish brown tinge and do not completely



Fig. 110 — Rosacea-like tuberculosis (Lewandowsky) Note spots which become more distinct under glass pressure. (Courtesy Division of Dermatology Department of Medicine, University of Chicago.)

fade under the pressure of glass. The diascope does not however show the transparent apple jelly colored lupus nodule as in lupus millaris which it resembles. There may be some pustulation cyanotic erythema and a certain amount of telangiectasias but not as marked as in rosacea. Scaling is sometimes present.<sup>205</sup>

<sup>200</sup>Lewandowsky F Rosacea-ähnliche Tuberkulide des Gesichts, Cor-Bli f Schweiz Ärzte 47 1240, 1917

<sup>201</sup>Wilde L J and Granger F H Rosacea-like Tuberculosis (S Case) Arch Dermat & Syph 31 174-180 1933

<sup>202</sup>Michelson H H and Winter L H Tuberculosis of the Face Arch Dermat & Syph 29 230-258, 1924

<sup>203</sup>MacKee G M and Paulsen M B Rosacea-like Tuberculosis of Lewandowsky Arch. Dermat & Syph 31 186-178, 1915



The microscopic structure is tuberculoid. No bacilli seem to have been found in the lesions so far. The patients are usually though not always <sup>74</sup> highly sensitive to tuberculin which is in contrast to the reaction in lupus miliaris. Visceral or other cutaneous tuberculosis, mostly of benign character was found in a fraction of the cases. Though still rare rosacea like tuberculosis is a relatively frequent form in America <sup>75</sup>

## CHAPTER XI

# DERMATOSES WITH CLAIMED BUT STILL CONTROVERSIAL TUBERCULOUS ETIOLOGY

### Erythema Nodosum

Erythema nodosum is a uniform syndrome characterized by an acute eruption of cutaneous and subcutaneous nodules together with systemic symptoms, especially fever. The nodules are mostly found in the tibial areas, less often on the extensor surfaces of the forearms and rarely on the face.<sup>722</sup> They are not very numerous from a few to about thirty varying from pea to walnut size sometimes moderately raised above the skin level. They are quite painful to the touch. The more superficial lesions are pink to red and undergo a change of colors which resembles bruises (erythema contusiforme). There is little tendency to coalesce. The nodules appear in several crops each of which takes about 1½ to 2 weeks to heal. The entire attack may last from three to six weeks or longer. Recurrences occur frequently.

The outbreak is often preceded and accompanied by fever, respiratory and gastrointestinal symptoms and pains in the muscles and joints which are sometimes swollen. The prognosis of the dermatosis, as such, is favorable.

The incidence shows a marked preponderance of children and adolescents over the adult and of the adult female over the male.<sup>723</sup> Erythema nodosum is seen more frequently in the cold season. There seems to be a high susceptibility of the nordic races.

There are many reasons to relate erythema nodosum with a tuberculous infection.

*Tubercle bacilli* have lately been detected more frequently in the lesions rarely and not<sup>724, 727-29</sup> undisputedly in microscopic sections but more often by successful inoculation into the guinea pig.<sup>27, 726, 729</sup> Debré, Mignon, Mallet<sup>725</sup>

Literature up to 1929, see P. Tachas.<sup>726</sup>

<sup>722</sup>Tachas, P. Erythema contusiforme and Nodosum, *Handb. d. H.* Ok. 8, 2: 584-585, 1925.

<sup>723</sup>Harckar, A. J. and Morris, H. E. Erythema Nodosum of Face, *Arch. Dermat. & Syph.* 43: 802-803, 1911.

<sup>724</sup>Milham, H. and Frederick, L. Skin Tuberculosis, *Review of Recent Literature*, Paris 1924, 1: 9-27, 979.

<sup>725</sup>Yoshida, A. E. Tuberculous Primary Infection of the Skin and Secondary Erythema Nodosum, *Arch. Dermat. & Syph.* 7: 68-69, 1911; 70: 1936; *Id.* 84: 643.

<sup>726</sup>Kerns, A., Chetailier, P., Lévy Brühl, M. and Coenil, L. Sur la présence du bacille de Koch verus dans les lésions cutanées et dans le sang d'un malade en plein accès d'erythème noueux, *Compt. rend. Acad. de Biol.* 112: 961-963, 1922.

<sup>727</sup>Lévy, A. A. Existence d'*Mycobacterium tuberculosis* dans les nodules de l'erythème noueux, *Compt. rend. Acad. de Biol.* 118: 310-312, 1924.

<sup>728</sup>Guéret, A. and Freese, R. Recherches bactériologiques sur l'erythème noueux, *Bull. Soc. franç. de dermat. et syph.* 45 (1): 1100-1111, 1929.

<sup>729</sup>Debré, R., Mignon, M. and Mallet, R. L'examen radiologique du thorax au cours de l'erythème noueux, *Bull. Soc. franç. de dermat. et syph.* 46 (1): 1112-1115, 1930.

found tubercle bacilli in the lesions in 3 adults and 3 children. These authors were unable to detect any pulmonary changes.

The *tuberculin reactions* in children and young adults were positive in over 90 per cent and more strongly positive than in control groups.<sup>792</sup> There are series of many hundreds of observations available.<sup>792-796</sup> In a number of instances the test was known to have been negative before the outbreak of erythema nodosum and was observed to become positive.<sup>794-795</sup>

The *provocation* of erythema nodosum<sup>799</sup> or at least of new lesions by tuberculin tests has been reported by Kropatchev and Veraner.<sup>800</sup> Wallgren<sup>801</sup> saw erythema nodosum after Calmette-Guérin vaccination. Yet it should be emphasized that in large series<sup>798</sup> 3 to 8 per cent of the cases have been definitely declared tuberculin negative.

*Simultaneous manifestations of tuberculosis* have been discovered in many instances. Prag<sup>793</sup> saw roentgenologic pulmonary changes in 91 per cent of his 157 cases; other authors in about 50 per cent.<sup>794-802, 804</sup> Few writers found the lungs involved in only a minority of their<sup>807</sup> cases.<sup>803</sup>

The pulmonary involvement was usually interpreted as recent or primary.<sup>791</sup>

A dense and enlarged hilus, tracheobronchial lymphadenopathy, peribronchial infiltration, pleural exudate or frank hyperplastic tuberculosis are the usual findings. The lymph node enlargement was more often bilateral than unilateral and the pulmonary infiltration was unilateral in about 50 per cent of the affected cases.<sup>809</sup> The relatively benign character of the hilar reaction is sometimes shown by its complete disappearance in a short time.<sup>80</sup>

<sup>792</sup>Bohner, P. L. Erythema Nodosum in the Adult. Nord. med. tidskr. 13: 231-243, 1937. Eri. 51: 454.

<sup>793</sup>Prag, A. B. Erythema nodosum. Hygiea, Stockholm 88: 804-801, 1933. Eri. 44: 164.

<sup>794</sup>Giersten, C. 63 Cases of Erythema Nodosum. Acta med. Scandin. 23: 57-110, 1934; Eri. 59: 246.

<sup>795</sup>Landorf, N. Tuberkulinnegatives Erythema nodosum. Acta paediat. 17: 180-187, 1933. Eri. 51: 254.

<sup>796</sup>Comby, J. A propos de l'érythème noueux. Bull. et méém. Soc. méd. d. hôp. de Paris 86: 1740-1742, 1934. Eri. 57: 678-679, 1937.

<sup>797</sup>Stavropoulos, J. Quelques considérations sur un cas d'érythème noueux. Bull. Soc. pédiat. de Paris 23: 545-560, 1935.

<sup>798</sup>Batboox, I. and Berthet, E. Un cas de primo-infection tuberculeuse ou érythème noueux chez une fillette de onze ans. Bull. et méém. Soc. méd. d. hôp. de Paris 81: 805-810, 1935.

<sup>799</sup>Ostanes, L. M. Rottler, E. A. and Paequalini, M. Q. Erythema Nodosum as Symptom of First Tuberculous Infection in Adults. Rev. Asoc. méd. argent. 49: 915-922, 1935. Eri. 56: 582.

<sup>800</sup>Lafosse, P. Erythème noueux chez une tuberculeuse: près des injections de tuberculine. Rev. de la tub. 1: 461-462, 1935.

<sup>801</sup>Kropatchev, A. N. and Veraner, V. V. Erythema Nodosum in Small Children. Soviet. pediat. N. 12: 67-68, 1936. Eri. 56: 59.

<sup>802</sup>Wallgren, A. Erythema nodosum nach Calmette-Injektion. Svensk. llt.-tidn. pp. 1207-1209, 1932. Eri. 44: 300.

<sup>803</sup>Stall, S. Erythema Nodosum Språkligt en celok. lsk. 35: 146-153, 1933. Eri. 43: 306.

<sup>804</sup>Giersten, C. Four Cases of Erythema Nodosum and Frökinfiltrat. Acta med. Scandin. 82: 53-65, 1934. Eri. 49: 247.

<sup>805</sup>Hazeburg, E. H. and Kropatchev, A. Etiology of Erythema Nodosum in Children. Borba. tuberk. 11: 112-115, 1931. Eri. 50: 61.

<sup>806</sup>Fauri, O. Beitrag zur Ätiologie des Erythema nodosum. Arch. f. Kinderh. 88: 295-301, 1931.

<sup>807</sup>Paul, L. W. and Pehle, E. A. Erythema Nodosum. Medica and Pulmonary Character. Radiology 27: 121-127, 1936.

<sup>808</sup>Aplak, W. W. Pathogenesis of Erythema Nodosum With Special Reference to Tuberculosis, rickettsial Infection and Rheumatic Fever. Arch. I. t. Med. 59: 85-81, 1937.

<sup>809</sup>Kerley, P. The Etiology of Erythema Nodosum. Brit. J. Radiol. 10: 196-204, 1937.



Fig. 111 — Erythema nodosum.

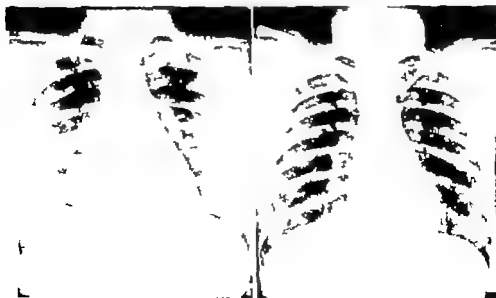


Fig. 112 Erythema nodosum. *Left* marked enlargement of the mediastinum and hilar lymph nodes. *Right* four weeks later. There is no demonstrable associated pulmonary disease. (From Peppel and McNamee. *New England J Med*.)

The lung changes have quite frequently been interpreted as a primary complex.<sup>84</sup> This is in line with the fact that fresh pulmonary changes are mostly encountered in young individuals. It is of special interest that young adults who by their negative tuberculin tests show that they have so far escaped tuberculous infection are more likely to get erythema nodosum on exposure to tuberculous infection than are controls. These persons usually become tuberculin positive in the course of the disease. This has been demonstrated in student nurses<sup>85</sup> and newly inducted soldiers.<sup>86</sup> Such and similar cases<sup>87</sup> carry much weight against the argument that a positive tuberculin reaction does not necessarily have to be related to erythema nodosum.<sup>784</sup> If it is true that erythema nodosum is rare in lung sanitariums this could be explained by the fact that most cases in these institutions are no longer in the early stages. Erythema nodosum has been seen to appear in the presence of extrapulmonary tuberculosis e.g. a cold abscess of the neck,<sup>88</sup> or of the breast<sup>89</sup> or after the surgical severing of pleural adhesions.<sup>90</sup>

Tubercle bacilli in the blood of patients with erythema nodosum have been demonstrated quite frequently<sup>91-93</sup> (12.5 per cent Saenz and Broca after Millan and Brodier<sup>780</sup> L. Nékám Jr.<sup>92</sup> in a case of so-called typhobacillosis). They do not prove conclusively the tuberculous etiology of the skin lesion since bacillemia is frequent in tuberculosis but they are a valuable support of a hemato-genous pathogenesis.

Tubercle bacilli have been demonstrated in the gastric juice especially of children with erythema nodosum<sup>94-96</sup> and also in the urine (Ramel after Millan and Brodier<sup>780</sup>). To these findings applies what has been said of the etiologic value of the bacillemia.

<sup>84</sup>Punch, A. L. Erythema Nodosum. Etiology. Lancet 2 10-11 1941

<sup>85</sup>Tornell, E. Untersuchungen von Keimerythemenfällen und ihrer Umgebung in der Fürsorgeklinik. N. Nat. Tuberk. Kvkr. 36 2-12 1935 226-231 176

<sup>86</sup>Debré, M. Erythème noueux et tuberculose. Bull. Soc. franç. de dermat. et syph. 48 11 1091 1096 1933.

<sup>87</sup>Gordon, H. Case of Tuberculous Infection With Erythema Nodosum. Bri. J. Dermat. 45 60-71 1933

<sup>88</sup>Penny W. M. Erythema Nodosum. Brit. J. M. 23 140, 1931

<sup>89</sup>Oestre, P. and Bernard, J. Erythème noueux et néphrite. pré-éclosion de tumeurs des testicules. Bull. et mém. Soc. méd. d. Hôp. d. Paris 88 1090-1093 1934

<sup>90</sup>Maschal, R. Tuberkelbacillen im Blut bei Erythema nodosum (Negativer Fluores bei Tuberkulose od. Erythema Nodosum). Verhandl. d. 6. int. oph. naturf. Gesellsch. p. 442 1933

<sup>91</sup>Palawan, O. Oomsansky V. and Ducas, P. Erythème noueux et tuberculose. Bull. Soc. pédiat. de Paris 28 452-454 1930

<sup>92</sup>Varanjo, P. Leber Tuberkelbacillen bei Erythema nodosum im Kleinkinder. Zschr. f. Tuberk. 71 11 16, 1934

<sup>93</sup>Hess, K. Erythema Nodosum mit Tuberkelbacillen im Hist. Hospitalbild 761 845-852 1932 224 67 713

<sup>94</sup>Akós, J. L. Fall von Landowsky'scher Typhobacillosis od. Erythema nodosum. Klin. Wchnschr. 22 1361 1496 1934

<sup>95</sup>Gokhale, A. A. Pathogenesis des Erythema nodosum. Monatschr. f. Kinderh. 81 219-267 1933

<sup>96</sup>Wall, J. Erythema Nodosum in School Children. Canad. med. Assn. J. 2 445-448 1931 214 66 7 1

<sup>97</sup>Politz, J. Tubercle Bacilli in the Gastric Juice from 100 cases. J. Cut. 22 363-395 1932

Case of E

While the prognosis of the dermatosis itself is good *severe and even fatal tuberculosis* has in a minority of the cases been seen (27 per cent,<sup>792</sup> 12 per cent,<sup>804</sup> 14 per cent<sup>825</sup>) to follow erythema nodosum.

Tuberculous meningitis,<sup>796-800,827</sup> miliary tuberculosis and florid pulmonary phthisis<sup>800</sup> have been reported occasionally. The most experienced observers agree that every case of erythema nodosum should be watched until the return of normal temperature and normal sedimentation rate.

The Scandinavian writers have often emphasized the *public health* aspect of erythema nodosum.<sup>811,821,822</sup> They regard erythema nodosum especially in school children as an indicator of an open source of tuberculosis in the surroundings. A school mate,<sup>823</sup> a family member or a coworker has time and again been found to spread tubercle bacilli which may account for the tuberculous infection by which erythema nodosum seems to be caused. After erythema nodosum children should remain in bed for several weeks and should be kept from school until all danger of acute tuberculosis can be safely disregarded.<sup>81</sup>

Small epidemics of erythema nodosum in hospital wards, boarding schools and families<sup>828</sup> have been observed several times and the source of the tuberculous infection has often been found.<sup>806,827</sup>

After the remarkable evidence which has been produced particularly by the Scandinavian authors it must be accepted that a varying and often large portion of the erythema nodosum eruptions is due to tuberculosis in the early stages particularly in juveniles at the time of the development of skin allergy.<sup>826</sup> The allergic pathogenesis finds fresh support in the parallel and more clear-cut cases of erythema nodosum in coccidioidomycosis (which see). Here the conditions are less complicated because most of the patients have never been infected and do not come from infected surroundings. In coccidioidomycosis the ery-

<sup>792</sup>Léonard E. Boquet, Y. and Galliano B.: Le pronostic Gogné d. l. érythème noueux, Arch. d. méd. d. enf. 30: 21-30 1927.

<sup>793</sup>Eckert, R. J.: Ueber Erythema nodosum ad Pleuritis concomitans in der Krankengeschichte der Lungentuberkulose, Act. obere Scandin. 6: 78-89 1922.

<sup>794</sup>Stekla, J. H.: Erythema Nodosum and Tuberculosis Arch. Derm. & Syph. 3: 28-31 1921.

<sup>795</sup>Sidic, D.: Meningeale Reaktion bei Erythema nodosum, Monatsschr. f. Kinderh. 67: 255-263, 1936.

<sup>796</sup>Kubacki, T.: Ankieta odc Erythema nodosum bei Kindern, Pediat. polska 12: 416-430 1932, Ery. 44: 676.

<sup>797</sup>Léonard M. E.: L'érythème noueux chez l'enfant, Bull. Soc. franç. de dermat. et syph. 46: 11 1945-1949 1936.

<sup>798</sup>Chen, C.: Ein Erythema nodosum-Endemie in einer Spitalabteilung, Monatsschr. f. Kinderh. 88: 241-258, 1923.

<sup>799</sup>Krahn, H.: Das Kostererythem, ein Warnungszeichen, Z. N. Tuberk. Keim 36: 13 1933, Ery. 51: 661.

<sup>800</sup>Landau, A.: Multiple cases of Erythema Nodosum in a Class of School Children, Arch. Dis. Childhood 7: 77-82 1932.

<sup>801</sup>Branson, K. F., Hardman, R. P. and Hiles, W. H.: Erythema Nodosum and Tuberculosis, Canad. J. Pub. Health 28: 437-54 1937.

<sup>802</sup>Krahn, H.: Erythema Nodosum Nord med. Mskr. 4: 330-336 1922, Ery. 47: 717.

<sup>803</sup>Wells, A.: Tubercular Etiology of Erythema Nodosum, Rev. argent. dermatol., 28: 227-229, 1932, Ery. 48: 604.

<sup>804</sup>Landau, A.: Schalephende on Erythema nodosum on lak-tiki, pp. 1419-1420 1932, Ery. 41: 15.

<sup>805</sup>Gendron, A.: Erythème noueux et miliary épidémique. Leur partition fréquente au moment de la primo-infection tuberculeuse, Bull. et mémo Soc. méd. d. Hôp. d. Paris 47: 947 1931.

<sup>806</sup>Léonard M.: L'érythème noueux. Faits étiologiques et cliniques, Bull. Soc. franç. de dermat. et syph. 43: 11 1946-1947 1937.

thema nodosum appears after the primary lung infection has produced allergy. The term "autogenous tuberculin reaction"<sup>33</sup> well expresses the pathogenetic theory. Some authors call erythema nodosum the exanthem of tuberculosis. This, too, regards the eruption in the light of the general observation that the beginning of the secondary phase of an infectious disease is often marked by an exanthem. The histologic findings sometimes show tubercloid structure but more often nonspecific inflammation especially around the veins. The lack of eosinophiles is an argument against an allergic pathogenesis.<sup>34</sup> The scarcity or the lack of tubercle bacilli in the lesions cannot be used as an argument against a tuberculous etiology since it may be explained by the strong defense which has developed and for which the positive tuberculin tests are proof. While especially in children and in cooler climates the important part which tuberculosis plays seems certain it needs to be emphasized that erythema nodosum has been seen in a great number of other infections<sup>35</sup> e.g. *ulcus molle*<sup>36</sup> lymphogranuloma inguinale Boeck's sarcoid coccidioidomycosis, trichophytosis *ulcus vulvae acutum* (Popoff 1938 after Pautrier<sup>34</sup>) (Samek and Fischer after Pautrier and Woringer<sup>37</sup>) syphilis leprosy measles and rheumatic fever as well as a drug eruption and finally without any apparent cause. The knowledge of the varied etiology of erythema nodosum invalidates an argument against a purely tuberculous etiology namely the cases which are numerous in some series in which by no method even by autopsy in some instances could tuberculous infection be found.<sup>38</sup>

The variations in the analyses are remarkable. Poppel and Melamed<sup>39</sup> found in a New York series only 4 out of 88 cases associated with tuberculosis. Ramel<sup>40</sup> believes that idiopathic erythema nodosum is always, in the child as well as in the adult the cutaneous manifestation of a tuberculous bacillemia. It seems best to regard erythema nodosum as a *clinical* rather than an etiological entity however the important role of tuberculosis especially in children cannot be denied.

Erythema exudativum multiforme has been suggested to be caused by hematogenous tuberculous infection.<sup>41 42</sup> English investigators<sup>43 47</sup> were unable to duplicate the guinea pig inoculations. The idea cannot be considered established except possibly for some cases of the Landouzy type of tuberculous

<sup>33</sup>Kroberg H. Erythema Nodosum and Tuberculosis. *Ann J Dis Child* 46: 1297-1307 1923

<sup>34</sup>Graybi S. Erythema Nodosum. *Bull Soc franç de dermat et syph* 48 III: 1073-1078 1914

<sup>35</sup>Pautrier L. M. Ulmo A. and Baumstark M. P. L'erythème noue au cours de diverses infections. *Bull Soc franç de dermat et syph* 48 II: 1207-1223, 1933

<sup>36</sup>Pautrier L. M. Woringer Fr. and Kern, R. Erythème papuleux circiné. *Bull Soc franç de dermat et syph* 48: 183-18 1933

<sup>37</sup>Poppel, M. H. and Melamed, A. M. Erythema Nodosum. *New England J Med* 227: 225-230, 1942

<sup>38</sup>Ramel, E. L'erythème exudaif multiforme. *Rapp Congr Dermatologistes Langue franç* pp 55-104 1929

<sup>39</sup>Dufour A. Deux cas d'ypothérilliose ou érythème polymorphe. *Lyon méd* 1930 I: 86-92

<sup>40</sup>Percival C. H. and Gibson H. I. Etiology of Erythema Exudativum Multiforme. *Brit J Dermat* 53: 327-343 1951

<sup>41</sup>Hallam, R. and Edington J. W. I. Evidence of Altered Tuberculous Etiology of Erythema Exudativum Multiforme (Heber). *Brit J Dermat* 55: 133-141 1953

bacillemla.<sup>54a</sup> Erythema multiforme and other exanthematic erythemas have been seen in association with erythema nodosum (Debré after Millan and Brodier<sup>78b</sup>)



Fig. 13.—Severe, partly bullous erythema exudativum multiforme with typical erythema nodosum on the legs. Toxiclike acute polyarthritis. Recurring attacks in spring.

**Initial Exanthems.**—In infantile tuberculosis ephemeral and inconspicuous morbilliform roseolar urticarial or erythema multiforme-like exanthems on the arms and legs have been observed occasionally by some authors and quite frequently by others. They may appear at the transition of the pre-allergic into the allergic phase of pulmonary tuberculosis<sup>54a, 60i</sup> i.e. about two months

<sup>54a</sup>Lenoir, F. E. Cutaneous Tuberculosis and General Medical Diagnosis, Ann. Int. Med. 8: 1274-1291, 1935.

<sup>60i</sup>Umbreit, A. Das Erythema (Frühexanthem) der kindlichen Tuberkuloseinfektion. München med. Wchnsch. 78: 823-837, 1937.

<sup>60ii</sup>van Mieris, H. Tuberkulöses Frühexanthem, Wien. klin. Wchnsch. 1934 II: 1091, 1093.

<sup>60iii</sup>Kundratitz, K. Das Frühexanthem der kindlichen Tuberkuloseinfektion, Wien. klin. Wchnsch. 1938 I: 921, 925.



after the infection. These exanthems being connected with the early allergic phases have been seen mostly in children. They are explained along the same lines as erythema nodosum.



Fig. 114.—Erythema exudativum multiforme. (Courtesy Dr. M. Jensen.)

Lichen nitidus<sup>320</sup> consists of pinhead sized glossy light colored superficial papules which most often occur on the penile skin. The lesions develop slowly and without any characteristic changes. They may stay for years. The microscopic picture is that of an almost too typical tubercle just below the epidermis with many Langhans cells and little necrosis. In a number of cases coincidence with pulmonary or cutaneous tuberculosis has been observed<sup>321</sup> but the tuberculous nature of the dermatosis is still controversial.

Granuloma annulare (Radcliffe (rocker) is characterized by hard yellow white almost flat papules arranged in coin-sized or larger rings most often on the dorsa of the hands rarely on the arms or elsewhere on the body. The course is slow and may become arrested at any stage. There are no complications or other changes than spontaneous regression sometimes after many years. The microscopic picture shows a deep-seated granuloma with central necrosis rarely<sup>322</sup> with a marked tubercloid structure.<sup>323</sup>

<sup>320</sup>Malak P. Ueber eine neue knochenformige Hauteruption. Lichen nitidus. Arch. f. Dermat. u. Syph. III 11 907.

<sup>321</sup>Rauch. Granuloma A. annulare. Zbl. II 401 1924.

<sup>322</sup>Jacobi F. Granuloma Annulare. Handb. d. H. Gik. 10, 794-815, 1921.

J. Jadassohn<sup>66</sup> and later his pupils (Martenstein and Knoll<sup>67</sup>) were impressed by the frequently negative tuberculin reactions in granuloma annulare in spite of many facts which pointed toward a connection with tuberculosis. They felt that granuloma annulare should be grouped with other positive allergic tuberculous conditions especially Boeck's sarcoid. Michael<sup>68</sup> reviewed 86 cases from the literature and found a definitely lower percentage of positive reactions than is found in the population at large. Tubercle bacilli have only exceedingly seldom been found in the lesions<sup>69</sup> the guinea pig inoculations being just as unsuccessful as the microscopic examinations. Combinations with pulmonary and other tuberculosis has been seen only in 16 to 20 per cent.<sup>66</sup> Tuberculin has had a healing effect in a number of cases and has occasionally provoked lesions.<sup>66</sup> The strongest argument against a tuberculous etiology is furnished by a number of cases in early childhood without tuberculosis and with negative tuberculin reactions.<sup>66, 70</sup> Granuloma annulare is probably a clinical reaction common to different agents of which the tubercle bacillus is only one. Some authors believe in a toxic etiology.<sup>66</sup>

### Boeck's Sarcoid (Benign Military Lupoid)

Boeck's sarcoid is a rare systemic disease involving predominantly the skin, the lungs, and the bones.

The trouble usually starts insidiously and takes an extremely chronic and unusually benign course. The original description of Boeck distinguished three types characterized by small disseminated cutaneous nodules or papules by larger and more grouped nodules, and by diffuse sometimes very extensive infiltrated plaques. With the greater number of cases published transitional and other varieties have become known and cases without skin involvement have been recognized. It is now believed that the skin participates only in about half of the cases (Voshein and Bonnevie after Leitner<sup>70</sup>).

The clinical feature which connects the nodules of varying size and shape is the diascopic appearance of small yellowish spots which resemble lupus lesions but are smaller and less transparent. These lupoid spots, which are responsible for the name benign military lupoid, may coalesce into larger areas. The small nodules are usually numerous giving the impression of an exanthem while the large nodules occur in smaller numbers. The lesions which are present simultaneously are in various stages of development. In some the skin may still be of normal color while in others definite lupoid red or brownish discolora-

<sup>66</sup>Jadassohn J. *Sarcoide und Lupus pernio*. *Kor. H. Schwerts Arch.* 64: 1474-1477 1914.

<sup>67</sup>Michael J. *Etiology of granuloma annulare with special reference to the tubercle bacillus*. *Theory Arch. Derm.* 3: 391-194, 395 1922.

<sup>68</sup>J. Jadassohn J. *Relationship of Tuberculosis and Granuloma Annulare*. *Dermatologica* 22: 196-197 1911.

<sup>69</sup>Knoll W. F. *Die Tuberkulose als Ursache der Granuloma Annulare*. *Brit. J. Derm.* 41: 67-6 1929.

<sup>70</sup>Leitner H. *Die Granuloma Annulare*. *Beitrag zur klin. u. dermat. et. 21* 1931.

<sup>71</sup>Hahn H. F. and Ingram John T. *Granuloma Annulare*. *Brit. J. Derm.* 47: 219-242, 1935.

<sup>72</sup>Leitner H. *Die Morben Heiler Boeck-Schaumann Haut.* 1932, Braunschweig.



Fig. 115.—Borck sarcoïd. Ring-shaped lesion with trophic center. (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)



Fig. 116.—Borck sarcoïd. Ring-shaped lesion under pressure. (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)



have been seen in some instances of lupus vulgaris (F Koch<sup>223</sup>). The different appearance of tuberculosis of the bones is emphasized by Naegeli<sup>224</sup>.

*Lymphadenopathy* is a common feature. The peripheral as well as the visceral lymph nodes especially those at the hilus are frequently enlarged. Schumann<sup>225</sup> found specific sarcoid tissue in the tonsils in all of his cases, and there is enough autptic evidence that practically all organs may become the site of hematogenous metastases<sup>226</sup>. Marked monocytosis sometimes as high as 40 per cent is a frequent though not invariable sign which Pinner<sup>227</sup> believes to be the hematological manifestation of a monocytic proliferation which also leads to the epithelioid granulomata.

It seems that sarcoid is relatively frequent in the American Negro<sup>228</sup>.



Fig. 117 — Borek's sarcoid. (Courtesy Dr. M. Jeanner.)

The microscopic structure of the lesions is better characterized by the term noncaseating tuberculosis<sup>229</sup> than by the rather vague word sarcoid. Dense foci of epithelioid cell tubercles are separated by areas of connective tissue. There is no caseation and little or no lymphocytic infiltration surrounding the lesions so that the apt term "naked tubercle" has been used. Giant cells may be found.

<sup>223</sup>Koch, F. Oculis hereticum multiplex cystoides (Jüngling) bei Lupus vulgaris, Dermat. Wchnschr. 1835 11 918-921.

<sup>224</sup>Naegeli, A. Sur les altérations osseuses dans la maladie de Heister Boeck, Bull. Soc. franc. de dermat. et syph. 41 1818-1826 1904.

<sup>225</sup>Schumann, R. Henna oculo-oculosa (Sarcoid) in Negroes, Arch. Dermat. & Syph. 20 54-73 1924.

According to Pinner tubercle bacilli have been found in the lesions 25 times. This is a small percentage but considering the law of Jadassohn and Lewandowsky the scarcity of microorganisms must be expected in tuberculoid structures and cannot be interpreted against the etiology in question. The fact that in a considerable number of instances tubercle bacilli have been demon-

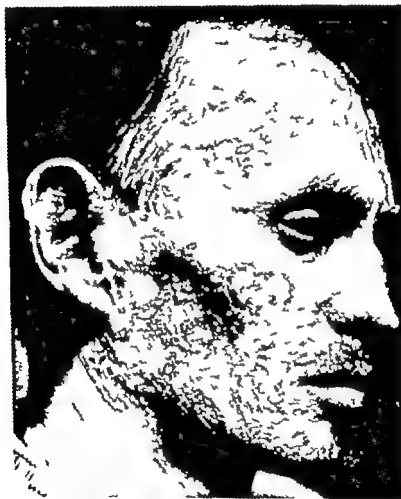


Fig. 1. Boeck's sarcoid. Courtesy Dr. M. Zinner.

strated in the lesions is a good argument for the tuberculous etiology of Boeck's sarcoid. Kunkel<sup>10</sup> showed that during the first days of crop of typical Boeck's sarcoid tubercle bacilli were numerous in the full erythematous lesions. There were peripustular foci of non-specific inflammation. Around the eleventh day the acid fast bacilli became scarce and epithelioid cells began to group together.

<sup>10</sup>Kunkel: Die A. Inguetation des Boeck'schen Sarkoids. Beitrag zur Frage der Classification dieser Dermatosen. Arch. f. Derm. Syph. 121: 22-23, 1931.

On the thirty-sixth day the typical sarcoid structure with epithelioid cell tubercles and giant cells was fully developed but no bacilli could be found. In the early stages the blood too contained tubercle bacilli<sup>87</sup> (see also Leitner<sup>88</sup>).

The tuberculin reaction is negative often even to 1 mg. of tuberculin or only slightly positive in the great majority of the cases. This *anergy* is much too frequent to be explained by freedom of tuberculous infection. Negative tuberculin reactions have even been found in cases of Boeck's sarcoid with frank tuberculosis.<sup>72, 74, 87, 87</sup> Zieler<sup>73</sup> however observed that the tuberculin reaction which had been negative in a case of lupus pernio became positive with the



Fig. 119 — Boeck's sarcoid (Courtesy Dr. M. Jeanneret)

outbreak of pulmonary tuberculosis. Lupus pernio is closely related to Boeck's sarcoid. Pinner<sup>74</sup> calls anergy an essential feature of the disease. Reactivity inhibiting substances in the serum so-called anticutins could be demonstrated in four out of eleven patients with sarcoidosis which is less often than anergy<sup>72</sup> but probably more frequent than in normal or tuberculous patients. In several animals e.g. rats dogs cats foxes and horses tuberculosis takes much more often than in man a sarcoid like course with epithelioid cell tubercles absence

<sup>87</sup>Martensel H. Sarkoid Boeck und Lupus pernio. Arch f. Dermat. Syph. 187: 70 1924.

<sup>88</sup>Jadassohn W. L'évolution tuberculeuse d. la maladie d. Boeck, Bull. Soc. franç. de dermat. et syph. 31: 1344-1347 1934.

of caseation energy and anticutins in the serum. This fact furnishes a parallel which can also be used in favor of a tuberculous character of Boeck's sarcoid.<sup>67</sup> Finally combination with and transition into frank tuberculosis has frequently been observed. St Epstein<sup>78</sup> found progressive pulmonary tuberculosis in about 12 per cent and less active forms in a still higher percentage<sup>67</sup> sometimes with disappearance of the sarcoid lesions. Appearance of the first lesion at the site of trauma<sup>80-82</sup> does not necessarily mean ectogenous infection since the trauma may lower the local resistance and attract the bacteria from the bloodstream. In this connection it may be mentioned that subcutaneous injections of many



Fig 120—Boeck sarcoid (Courtesy Dr Melamed)

substances especially oils may cause reactive changes of great similarity to sarcoid. The majority of the authors now seem to favor a tuberculous etiology of Boeck's sarcoid while dissenting writers, among them Kismeyer<sup>83</sup> who has wide experience with this rather rare disease hold that the disorder is a specific nosological and etiological entity. Kismeyer<sup>83</sup> bases his opinion on the too rare and in his opinion not always valid findings of acid-fast bacilli on the

<sup>67</sup>Boeckes F. Sarcoid and Tuberculosis—Case With Autopsy. *Arch. Dermat. & Syph.* 48: 800-871 1943

<sup>68</sup>Forrester H. R. and Wieder L. M. Sarcoid (Boeck Type). *Arch. Dermat. & Syph.* 32: 343 1930

<sup>69</sup>Gougerot H. and Hém, P. Tuberculose sarcoides hypodermiques par corps étrangers à la suite d'injections de vacchins subcutanés en excipient aqueux. *Bull. Soc. franç. de dermat. et syph.* 29: 1834-1837 1932

<sup>70</sup>Kismeyer A. Contribution à l'étude de clinique des sarcoides. *Bull. Soc. franç. de dermat. et syph.* 41: 1103-1107 1934

<sup>71</sup>Kismeyer A. Beitrag zur Ätiologie und Klinik des Boeckschen Sarcoids. *Hochschulz. 1932* 11: 1047-1079. *Zbl. H.* 837



benign course on a refutation of J. Jadassohn's theory of positive energy and other reasons\*. Some writers believe that the disease has the characteristics of a chronic bacillary granuloma with features relating it to tuberculosis, syphilis and also to leprosy<sup>273 284</sup> while Rabello Jr.<sup>285</sup> thinks that tuberculosis, leprosy and perhaps still another disease may produce Boeck's sarcoid. Arsenic has a distinct therapeutic influence. This fact has been used as an argument against the tuberculous etiology.

**Lupus Pernio.**—Lupus pernio is closely related to Boeck's sarcoid<sup>281 287</sup>. It manifests itself as ill-defined cyanotic, cutaneous and subcutaneous nonulcerative plaques most frequently found on the nose and cheeks with marked symmetric tendency. On glass pressure lupus-like spots can be demonstrated. This rare and chronic disorder affects mostly adults and is combined with bone alterations which resemble those found in Boeck's sarcoid. Histology and marked positive energy to tuberculin are further links to that disease and thus to tuberculosis.<sup>230 284 286-277-288</sup>

**Erythrodermia Exfoliativa (Pityriasis Rubra of Hebra)**—Universal redness, infiltration and scaling accompanied by lymphadenopathy may be a phase in many diseases e.g. leukemia, arsenic poisoning, psoriasis, eczema and many others. Jadassohn<sup>247</sup> in an analysis of 18 cases revealed that in at least eight pulmonary and other forms of active tuberculosis were present. Since then many such cases have been described.<sup>282</sup>

**Purpura Hemorrhagica**—The whole syndrome of hemorrhagic purpura, even purpura fulminans (Gaede et al.<sup>289</sup>) may be produced by tuberculous infection. Miliary tuberculosis of the spleen seems to be especially predisposing particularly in children.<sup>290 291</sup> Cases with a fulminating course of less than one day have been observed. The number of cases of mild and severe purpura occurring in many types of visceral tuberculosis is considerable so that coincidence is unlikely. Some purpuric spots could be shown to possess tubercular structure.<sup>292</sup> This corresponds to experiences with other purpuric infectious efflorescences e.g. the rickettsioses and bacterial meningitis. An old report of a finding of tubercle bacilli in purpuric skin lesions (Beinseide and River 1906 after Volk<sup>293</sup>) does not seem to have been confirmed more recently.

\*Similarly Lettner<sup>281</sup> in recent review interprets the negative tuberculin reactions against tuberculous etiology. He also questions the validity of some of the positive findings of bacille bacilli.

<sup>273</sup>Klimmeyer A. La maladie d Boeck. Sarcoides cutanées à lésions multiples, Préface de J. Darier. Paris, 1932, Masson & Co.

<sup>284</sup>Rabello J. E. Données nouvelles pour l'interprétation de l'affection de Boeck. rôle de la syph. A. d. dermat. et syph. 7: 571-597 1936.

<sup>285</sup>Kobayashi E. Lupus pernio mit Knochenveränderungen. Jap. J. Dermat. & Urol. 21: 1869-1873. Jid. 41: 1-3.

<sup>286</sup>Jadassohn J. Pityriasis rubra Hebra und ihre Beziehungen zur Tuberkulose, Arch. f. Dermat. Syph. 23: 911 1891. 24: 85 273 403 1892.

<sup>287</sup>Darier J. P. Pityriasis Rubra, Hebra) Arch. Dermat. & Syph. 18: 716-729 1924.

<sup>288</sup>Gaede M. H. and Vaughn, J. J. Miliary Tuberculosis With Purpura in Infancy. Am. J. Dis. Child. 42: 869-873 1931.

<sup>289</sup>Quick A. J. The Hemorrhagic Diseases and the Physiology of Hemostasis, Springfield, Ill. 1912 Charles C. Thomas.

<sup>290</sup>Weiner J. J. and Carter R. F. Acute Thrombocytopenic Purpura Hemorrhagica Associated With Tuberculosis (Miliary) of Spleen. pleurostoma With Recovery. Am. Surg. 22: 87-91 1911.

**Scrofulosis (Scrofula)**—Scrofulosis is a syndrome of nontuberculous inflammatory alterations in a child with tuberculosis predominantly of the lymphatic nodes of the neck and of the bones.<sup>192</sup> The characteristic combination of swollen or abscessed submaxillary or cervical lymph nodes, eczema especially



FIG. 1. *Erythroderma phlyctenularis*. (Courtesy Dr. M. Jansen.)

around the mouth blepharitis phlyctenules conjunctivitis otitis media and rhinitis used to be a most common sight in the pediatric clinics of Europe. Scrofulosis is today rare in America<sup>193</sup> and has also decreased in other countries. Landi<sup>193</sup> believes that scrofula is an infection with the bovine type of the tubercle bacillus. He explains the disappearance of scrofula with the pasteurization of milk. The tuberculin reactions in scrofulous children are strongly positive.

**Avian Tuberculosis**—Human infections with tuberculosis of birds, usually chickens may lead to severe systemic and cutaneous diseases which have re-

<sup>192</sup>Marian A. B. *La scrofula conception ancienne conception nouvelle*. Paris med. 11 12-20.

<sup>193</sup>LANDI, H. R. M. The Disappearance of Scrofula. *Am. Rev. Tuberc.* 31 193-201 1930.

resemblance to all known types of human tuberculosis but do not quite fit into the familiar pictures. Thus aphthous and septicemic, sarcoid gummatous and ulcerative forms have been described <sup>200 201 202</sup>

The diagnosis will rest on the chicken experiment, the positive avian tuberculin test and the bacteriological culture. The cases seem to be rare. However the diagnosis is important since specific tuberculin treatment has been effective in the cure of such patients (Löwenstein and Joannovic quoted by Urbach<sup>203</sup>)

### Lupus Erythematosus Chronicus

The term lupus erythematosus (erythemateux) was coined in 1851 by Cazenave in a clear differentiation from other forms of lupus as many destructive dermatoses were called. Cazenave (after the French text given by Paul Rich-



Fig. 122 —Lupus erythematosus discoides

ter<sup>207</sup>) describes this form of lupus as one which destroys superficially and which does not develop tubercles (which in Cazenave's time meant ulcerating nodules). The relationship of the disease which we now call lupus vulgaris to tuberculosis was then of course not yet understood because our present conception of tuberculosis which is based on the presence of the tubercle bacillus or its derivatives did not yet exist. In 1884 Robert Koch demonstrated by culture and animal experiment the tubercle bacillus in lupus vulgaris. After Koch the term lupus became definitely associated with tuberculosis. Despite the fact that Koch dealt

<sup>200</sup>Urbach, F. Das Krankheitsbild der Gefüßerkulose der Haut beim Menschen und beim Tier. Arch. f. Dermat. Syph. 187: 260-3, 1929.

<sup>201</sup>Löwenstein, E. Das Krankheitsbild der Hühnererkulose beim Menschen. Sch. et. med. Wchnsche. 2: 804-810, 1914.

<sup>202</sup>Karl W. Gefüßerkulose Verhandl. 9 Internat. Kongr. Dermat. 2: 269-273, 1924.

<sup>203</sup>Richter, P. Geschleib. der Dermatologie Handb. f. H. 11. Gk. 18, 3: 206, 1924.

with lupus vulgaris only his work had the effect of stimulating research to prove the hypothesis of a tuberculous nature of lupus erythematosus also.

The French dermatologists under Bessiers influence generally adopted the tuberculous etiology of lupus erythematosus while the majority of the German authors concerned with the question rejected this theory for a long time. Later on the Germans gradually and very reluctantly became more inclined to acknowledge the importance of tuberculosis in the etiology of lupus erythematosus.



FIG. 123 - Lupus erythematosus chronicus

In the lesions of lupus erythematosus the *tubercle bacillus* has rarely been demonstrated with the Ziehl-Neelsen stain<sup>229 230</sup>. In several instances acid fast bacilli closely resembling the tubercle bacillus have been found in the sediment from tissues destroyed with antiformin. The etiological significance of these findings must be considered doubtful because such para-tubercle bacilli have been found in many media and the antiformin method does not permit the differentiation of bacilli originating from the surface from those from the depth. In spite of negative control tests in normal skin<sup>231</sup> these antiformin findings have not been acknowledged as an etiologic proof<sup>700 699</sup>.

As far back as 1906 Gougerot succeeded in demonstrating the presence of the tubercle bacillus in the lesions of lupus erythematosus by means of an animal inoculation. These findings have been confirmed several times<sup>729 740</sup> though a great

<sup>229</sup>Friedländer, D. The Etiology of Lupus Erythematosus. Special Reference to Tuberculosis, *J. Cutan. & Genito-Urin. Dis.* 23: 417 1911.

<sup>230</sup>Viel, P. Lupus erythematosus (Carnoy) Handb. d. H. *Ok* 10: 1 647 194, 1921.

<sup>231</sup>Block, Br. and Fuchs, H. Chronic Lupus Erythematosus and Tuberculosis, *Arch. f. Dermat. Syph.* 115: 743 1913.

resemblance to all known types of human tuberculosis but do not quite fit into the familiar pictures. Thus aphthous and septicemic sarcoid gummatous and ulcerative forms have been described <sup>286 287,288</sup>

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<sup>287</sup>Löwenstein, E. Das Krankheitsbild der Hühnertuberkulose beim Menschen, Schwein und Welsch. Z. 2: 409-410, 1931.

<sup>288</sup>Karl, W. Gefäßtuberkulose. Verhandl. 9. internat. Kong. Derm. 2: 260-272, 1926.

<sup>289</sup>Richter, P. Geschichte der Dermatologie. Handb. f. H. u. G. 16, 2: 206, 1924.

observations carry as little weight in the discussion of the tuberculous etiology of lupus erythematosus as the successful treatment with tuberculin. One should also remember that nonspecific focal reactions have been seen after injections of many substances, e.g. gold milk and other foreign proteins sulphur etc.

It is important in the discussion of the tuberculous origin of lupus erythematosus to consider whether or not this condition is more frequently found in tuberculous than in nontuberculous individuals. The opinions on this are extremely contradictory. Goeckerman<sup>10</sup> denies that lupus erythematosus is substantially more frequently associated with tuberculosis (36 per cent) than other dermatoses (32 per cent). The number of authors who believe that lupus erythematosus is a disease of persons with tuberculosis especially pulmonary and glandular is large. Ehrmann and Falkenstein<sup>11</sup> claim that tuberculosis could be demonstrated in about 50 per cent of the acute cases of lupus erythematosus in about 80 per cent of the chronic cases of lupus erythematosus with acute exacerbation and in 98 per cent of chronic lupus erythematosus. Oro's<sup>12</sup> figures run similarly high. Pautrier and Schaaff<sup>13</sup> give 72 per cent. The most recent survey is that of St. Epstein<sup>14</sup> who examined 200 cases of lupus erythematosus in 7.2 per cent of which active tuberculosis of the lungs could be demonstrated by X-ray. This is much less than in cutaneous tuberculosis (16.1 per cent) but much higher than in the controls (3.7 per cent) which were taken of the syphilitic patients in the hospital.

On the other hand in a great number of cases it has been impossible to produce any evidence of tuberculosis either during life or post mortem. Of course the value of such negative findings is always limited because small foci can easily be overlooked. The complement fixation tests with the antigens of Beredka, Calmette, Ponndorf and others did not corroborate the tuberculous origin of lupus erythematosus.<sup>15</sup> Combination with skin tuberculosis such as lupus vulgaris, scrofuloderma or the so-called tuberculids has quite often been reported. Lewandowsky<sup>16</sup> wrote in 1916 that the reports about the combination of lupus erythematosus and tuberculids had lately become too numerous to be explained by coincidence. Since then these reports have multiplied. Practically every type of skin tuberculosis has been seen in combination with lupus erythematosus. Lupus erythematosus as well as skin tuberculosis being rare diseases, the number of reported combinations seem to exceed by far the rate of pure coincidence. Uebach<sup>17</sup> saw lesions of lupus erythematosus the diagnosis of which he secured by histological examination develop in the neigh-

<sup>10</sup>Goeckerman W. H.: Lupus Erythematosus discoides chronicus due to Tuberculosis? Arch. Dermat. & Syph. 2: 745-750 (1931).

<sup>11</sup>Ehrmann and Falkenstein F.: Lupus erythematosus, Arch. f. Dermat. Syph. 141: 405 (1922).

<sup>12</sup>Pautrier E. M. and Schaaff: Results of Systematic X-ray Examination of Lungs in 26 Cases of Lupus Erythematosus, Id. 56: 203.

<sup>13</sup>Stebbins K.: Komplexe-entzündungsreaktion bei der Tuberkulose mit besonderer Berücksichtigung der Haut- tuberkulose Die komplexe-entzündungsreaktion bei Lupus erythematosus, Acta derm. venerol. 7: 3: 5-2 (1925).

<sup>14</sup>Uebach E.: Lupus erythematosus in der Schenkel- Umgebung eines Scrofulid- Scrofuloderma, Id. 11: 290 (1924).

hood of a tuberculous fistula. Stühmer<sup>91</sup> saw true lupus nodules in the scar of lupus erythematosus. The rarity of such observations in America may be explained by the fact that cases of skin tuberculosis are only about one-tenth as frequent in North America as they are in Central Europe. As mentioned before lupus erythematosus is about as common in America as it is in Europe. This lack of parallelism seems to indicate that lupus erythematosus, in spite of many relations to tuberculosis is governed by another law than true tuberculosis of the skin.

Without going into detail it may be mentioned that evidence of similar character as that in favor of a tuberculous etiology has been produced in support of other bacteria syphilis mechanical trauma cold light and other agents.

Thus in spite of the great efforts which have been made the role of tuberculosis in the etiology of lupus erythematosus chronicus remains controversial.

### Lupus Erythematosus Acutus

The most important systemic relationship of lupus erythematosus exists in the rare cases in which the dermatosis either starts with an acute dissemination or where an apparently chronic lupus erythematosus changes its character and becomes acute (*Lupus erythematosus acutus* and *lupus erythematosus chronicus cum exacerbatione acuta*).

Transitional cases between all types of lupus erythematosus have been demonstrated. They prove the close relationship of the various types.

The acute form of lupus erythematosus seems to occur in all ages but the majority of the patients are those in the third and fourth decade.

The sex distribution of the acute forms has the ratio of three females to one male. This ratio is based on a review of 100 cases published in the last twenty years.

Many factors can change the character of chronic lupus erythematosus into the acute form. Known to have provoked acute lupus erythematosus are exposure to sun and to strong artificial light<sup>92-93</sup> bee stings applied for the treatment of arthritis<sup>94</sup> mosquito bites gold therapy trivial infections like otitis media<sup>95</sup> or such following tooth extraction<sup>96</sup> lymphangitis<sup>97</sup> polyarthritis<sup>98</sup> and physical and mental strain<sup>97</sup>. In many cases however the disease apparently begins without any such factors.

<sup>91</sup>Various authors. *Lupus erythematosus. Symposium on Arguments For and Against Tuberculous Nature, Dermat. Wehrsch 90* 1246-1256 1934.

<sup>92</sup>Rosbarck, A. C. Acute Disseminated Lupus Erythematosus. Five Fatal Cases, *Brit. J. Dermat.* 48 85-100 1933.

<sup>93</sup>H. Naum. *Lupus erythematosus*, *Zbl. IT* 768, 825.

<sup>94</sup>Wiem, J. H. Generalized Lupus Erythematosus and Intrabdominal Tumor *Am. J. Dis. Child* 28 125-13 1924.

<sup>95</sup>Grunt, O. Beiträge zur Klinik und Histologie des Lupus erythematosus acutus, *Arch. f. Dermat.* II pk 157 524-530 1924.

<sup>96</sup>Val, S. Pathogenese und pathologische Anatomie des Lupus erythematosus acutus, *Moskov. med. Z.* 91 1-9 1 29 *Zbl. B.* 125 193.

<sup>97</sup>Clark, F. H. and Warnock, A. W. *Lupus Erythematosus Acute Disseminated*, California & West Med 24 354-3 7 1926.

<sup>98</sup>O'Brien, R. Fatal Case of Lupus Erythematosus, With Post Mortem, *Brit. J. Dermat.* 27 223 1925.

<sup>99</sup>Eakman, M. F. J. Early Acute Lupus Erythematosus *Arch. Dermat. & Syph.* 28 845-807 1937.



Fig. 121.—*Lupus erythematosus scrotae* (Courtesy Dr. H. J. Janney)



Fig. 122. Subacute lupus erythematosus, seborrheic. Exacerbation after prolonged exposure to sunlight early in spring.



The onset may be sudden with chills high temperature and all the symptoms of an acute infection. However there are cases starting with relatively mild attacks of skin eruptions even without fever. Excessive fatigue is an outstanding complaint.

The most constant early cutaneous lesion is the appearance of sharply outlined red patches on the face. These *erythemas* are often arranged in butterfly or bat shape covering the nose and the malar prominences the ears especially the upper parts of the helix the chin and the neck. Here the erythema is often limited to the lower anterior part the neck which particularly in women is exposed to the light. The erythema is often but not always edematous or vesicular especially in severe cases. The rash can simulate erysipelas but the symmetry the development from a number of small individual erythematous lesions the comparative stability and the course will soon differentiate the two. In the edema the follicles appear more open creating an orange-peel like surface



FIG. 1A. Lupus erythematosus, acute dissemination after first prolonged exposure to sun. Spring scalp lesion with loss of hair and old open follicles.

The simultaneous appearance of lesions of the scalp and fingers is very characteristic. The so-called erythema perstans of the face may remain throughout the whole course of the disease. It may disappear and recur. The erythematous eruptions may spread over large areas even over the whole body surface. Exudative features like vesicles blisters and crusts sometimes create an eczematous impetiginous or even pemphigoid appearance. Hemorrhagic lesions mostly of small size have often been observed.

In some cases the skin lesions have a more exanthem like appearance described as a roseola or as a morbilliform rash. Often the skin lesions appear in crops which fade or heal and recur often after intervals of indefinite length. It is a definite characteristic of the dermatosis to "center" about the nose and neck. Here the lesions are redder more deeply infiltrated more constantly observed and healing with atrophy is more frequent than in other sites. "More or less acute oral and tonsillar infection" are not uncommon.

In acute lupus erythematosus the cutaneous eruption is *not* the most important part of the picture. It is the syndrome of a severe systemic infection or toxic reaction which determines the picture and the course. Continuous high fever is an almost regular symptom. General malaise and later on prostration and exhaustion are frequent.

Fig. 127

Fig. 128



Fig. 129.

Fig. 127 - Lupus erythematosus acutus (P's. les. of Dr. Rosenthal)

Fig. 129 Lupus erythematosus acutus. Detail of face. Not open follicles. Patient of Dr. S. Rosenthal.)

Fig. 128. Lupus erythematosus acutus. Effluvium capillorum during prolonged febrile disease. (Patient of Dr. S. Rosenthal.)

*Lymphadenitis vithrius* and more often arthralgia without true arthritis are other septic symptoms. The joint pains frequently accompany the acute exacerbations. The spleen is often enlarged.

*Nephritis* often with a high albumin content of the urine is one of the most constant and often early complications. *Retinitis albuminurica* has been seen several times. *Hematoporphyrin* in the urine is a frequent finding in acute lupus erythematosus especially in the severe cases. The photosensitizing effect of hematoporphyrin is well established.<sup>328</sup> *Colitis* and *enteritis* often not only cause diarrhea but severe abdominal pain which has caused unnecessary appendectomies in several instances.<sup>329</sup> *Endocarditis myocarditis* and *bronchopneumonia* are common and together with renal failure frequently the immediate cause of death.



Fig. 130. Lupus erythematosus acute. Not center of rash in neck area. Courtesy Dr. J. J. Ziemer.

The blood cultures done in a great number of cases of acute lupus erythematosus have usually been negative. Occasionally streptococci were found<sup>330</sup> and very rarely staphylococci and bacterium coli. These and some other findings probably are terminal or incidental. The largely negative blood cultures indicate toxemia rather than bacteremia.

Leukocytosis of 15 20 000 or more has been observed several times but it is the exception. Much more frequently the white count is low even as extremely low as 800. It has been emphasized<sup>331</sup> that even complications like pneumonia, pleurisy, nephritis and endocarditis failed to raise the low white count. The

<sup>328</sup>Deriaz F. and Baranetta J. *Akute Dermatosen Handb d H. Ch. 4* 1 124-186 1922

<sup>329</sup>Mease E. and Goldberg L. *Lupus Erythematosus. Visceral Lesions of the Dermis of Lupus*, 31 (The North America) 333 335

<sup>330</sup>Ostrouski. *Lupus erythematosus acutus* *Zbl* 25 139 1927

<sup>331</sup>Stelzner H. W. *Der Kollid. ad Aetiologia des Lupus erythematosus* *München med. Wochenschr.* 72 1023 026 1925

<sup>332</sup>Wendt H. *Lupus Erythematosus* *Int. med. Disease München med. Wochenschr.* 91 217 1911

granulocytes are the elements which suffer most while the lymphocytes prove to be more resistant so that a relative lymphocytosis may result. An eosinophilia is another frequent and unfavorable occurrence. The reappearance of the eosinophiles often accompanies improvement and remissions. Purpuric spots, petechial showers and thrombocytopenia are recognized features of the syndrome.<sup>323-324</sup> Wendt emphasizes that his patients with leukopenia, thrombopenia and purpura had not received gold treatment, which can cause similar lesions.

Secondary anemia is frequent. The sedimentation rate is often increased.



Fig. 131. Petechia in lupus erythematosus acutus.

Acute lupus erythematosus is a very dangerous disease in both its forms though the acute exacerbation of a pre-existing chronic discoid lupus erythematosus has a better chance to heal or to return to the chronic stage than have the primarily acute cases.<sup>325</sup> Out of 100 cases published from 1920 to 1940 at least 76 ended fatally. Recovery being rare only a few cases of the transition of true acute lupus erythematosus into the chronic discoid form have been observed.<sup>326</sup>

The gross pathologic findings consist of a variety of septic, renal, pulmonary and liver changes, splenic infarcts and muscular and valvular heart lesions.<sup>326</sup>

In 111 autopsies in acute lupus erythematosus (Gawulowski<sup>326</sup>) tuberculosis was the sole finding in somewhat more than 50 per cent. In less than 50 per cent there were no traces of tuberculosis, but usually another bacterial infection was present. Other experiences were similar.

<sup>323</sup>Row, E. and Pillsbury D. M. Acute Disseminated Lupus Erythematosus. *Systemic Disease Ann. Int. Med.* 23: 961-963, 1930.

<sup>324</sup>Kell, H. Lupus Erythematosus and Its Morphologic Variants With Particular Relation to Systemic Lupus Erythematosus. *Arch. Dermat. & Syph.* 24: 729-757, 1927.

<sup>325</sup>Oslen, C. M. and Adams, E. C. Six Autopsied Cases of Disseminated Lupus Erythematosus. *Am. J. M. Sc.* 206: 23, 1943.

<sup>326</sup>Gawulowski, K. Lupus erythematosus acutus. *Federative Acta dermat.* reserved 33: 1-29, 1939.

It is likely that the twenty cases of erythema with visceral lesions described by William Osler<sup>327</sup> in 1904 included cases of lupus erythematosus acutus. The outstanding lesions were purpura erythema colic nephritis and arthritis. There is little clinical or post mortem evidence of endocarditis.

The Libman-Sacks syndrome<sup>328, 329</sup> consists of a peculiar verrucous endocarditis differing from that in rheumatic fever mainly by the absence of Aschoff bodies. The patients are mostly young females. Six out of eleven had lupus erythematosus three more only erythema. Purpuric symptoms were common. Leukopenia and thrombocytopenia occurred. Pericarditis arthritis and nephritis were found in almost every case.

It has been pointed out that all the symptoms of lupus erythematosus acutus are rather fluctuating. It is likely though not yet certain that the Osler<sup>327</sup> erythema group and the Libman-Sacks<sup>328</sup> syndrome and acute lupus erythematosus form an entity which often but not always develops typical dermatomes. The fundamental and common pathology of the group can possibly be seen in the widespread vascular lesions of the finer ramifications described by Baehr, Klemperer and Schiffin<sup>330</sup>. These lesions consisting in capillary dilation endothelial proliferation a peculiar hyaline degeneration thrombosis and extravasation were found in all viscera in about 25 per cent of the cases but they were most frequent in the skin and in the kidneys. Glomerular changes of this kind make the thickened capillary wall appear rigid as if made of heavy wire. These 'wire loop' lesions which were present in more than 50 per cent of the cases and which have been often confirmed<sup>331, 332, 333</sup> are very striking. The authors emphasize that they have not seen them in any other human disease except perhaps in eclampsia. Similar lesions were found in horses which had been immunized by frequently repeated intravenous injections of live bacteria especially of the pneumococcus-streptococcus group.

More recently<sup>334</sup> a new conception based on observations of physicochemical alterations in the fibers and ground substance of the connective tissue has been developed.

<sup>327</sup>Osler W. The Erythema Group of Skin Diseases. *Am. J. Sc.* 127: 1, 1904.

<sup>328</sup>Libman, E. and Sacks, D. A Hitherto Undescribed Form of Valvular and Mitral Endocarditis. *Arch. J. Med.* 33: 701, 1934.

<sup>329</sup>Deliot, G. H. and Baehr, G. V. Lupus Erythematosus—So-called Libman-Sacks-Syndrome—Relation. *Dermatology Arch. Dermat. & Syph.* 33: 642, 1936.

<sup>330</sup>Baehr, G., Klemperer, T. and Schiffin, A. *Tr. A. Am. Physicians* 59: 139, 1939.

<sup>331</sup>Jacobs, S. Lupus Erythematosus Associated With Visceral Vascular Lesions. *Series of Autopsied Cases Bull. Johns Hopkins Hosp.* 80: 263-273, 1936.

<sup>332</sup>Deslaur, J. and Moutonnet. Acute Lupus Erythematosus Dissemintatus. *Ann. J. Dis. Child.* 53: 325, 1937.

<sup>333</sup>Klemperer, P., Pollack, A. D. and Baehr, G. Acute Lupus Erythematosus. *New York State J. Med.* 43: 2324, 1943.



Leprosarium in Carville Louisiana<sup>622</sup> Great numbers of lepers live in the Philippines and in Hawaii where under American administration important scientific observations have been made. The leper island of Culebra in the Philippines and the Kalihii hospital of the United States Public Health Service in Honolulu have in many ways become model institutions. Some authors think that leprosy existed in America before the voyage of Columbus.

**Etiology Contagion**—Leprosy is caused by the Hansen Neisser bacillus, an acid fast rod which in many ways is related to the tubercle bacillus. It stains best with the Ziehl Neelsen method but it is a little stouter and straighter more angular if bent and usually more numerous and more apt to form bundles than the tubercle bacillus.

**Culture** as well as progressive infection of animals, has not yet been accomplished in an entirely satisfactory and corroborated way. Though this has hampered elucidation of many phenomena the etiologic role of the Hansen Neisser bacillus has been sufficiently demonstrated by its constant presence in almost all leprosy lesions in the blood in the majority of the organs in about 50 per cent of the cases and in all secretions, as well as by its absence in other diseases and in healthy individuals from leprosy free surroundings.

Leprosy is a moderately contagious disease. The epidemiology is still contradictory. Most individuals according to Muir<sup>624-626</sup> nine out of ten seem to possess a high degree of resistance. This is demonstrated by many instances of persons who remained healthy in spite of exposure to massive infection over a long period of time. These were mostly family members who lived together with contagious lepers. Conjugal leprosy is not common and contagion by intercourse occurs rarely. Nurses and physicians caring for lepers have not very often become lepers. It is hard to decide how much credit must be given to sanitary measures and avoiding contact.

True congenital leprosy is rare. Rodriguez<sup>627</sup> did not find a single case in 871 children born of lepers in the Culebra colony. Many children in leprosy surroundings become infected early in life but many stay healthy.<sup>628</sup> Breast feeding is not an important factor in the transmission of leprosy from mother to child.<sup>629</sup> Contact with contagious lepers in close living quarters seems the main way of transmission but even under such conditions contagion does not invariably occur. The author saw a leper covered with tuberculous lesions who lived for 16 years in one room with his family all members of which remained healthy.

Though experienced leprologists believe that the leprosy bacillus does not live long outside the human body many authors are convinced that the disease can be carried by insects especially bedbugs and acari and a variety of fomites.

<sup>622</sup>Hopkins R and Faget G H: Recent Trends of Leprosy in the U. S. A. J. A. M. A. 126 977 943 1944

<sup>624</sup>Muir E: Importance of Natural Resistance in Leprosy. T. Far East A. Trop. Med. 2 231-247 1932.

<sup>625</sup>Muir E: Leprosy—Resistance and Typing of Skin Lesions. Leprosy Rev. 10 221 225 1929.

<sup>626</sup>Rodriguez J: Leprosy in the Philippines. J. M. H. 27 465 1929 21 115, 1026 J. Philippine Islands 31 A 6 40 192 6 43 1926 6 245 192 6 467 1928 Mon. Hly. Bull. Philippine Health Serv. 8 22 1929 8 702 1929 6th Congr. Far East A. Trop. Med. Tokyo, 1925. H. 609 1926.

among which bedding plays a major role. Airborne droplets from coughing and sneezing may carry the microbes<sup>21</sup> but the importance of this way of transmission is controversial. The infection of the nose with the fingernails is important. Leprosy is mostly a disease of the underprivileged classes intimately connected with dirt, poor housing, poor diet and other unsanitary conditions.

**Incubation. General Course, Types.**—The incubation period is extremely variable, the observations ranging from one week to as long as 32 years. The average may be one or a few years. Rodriguez<sup>22</sup> in observations of children of lepers in Cullion found it to be three years nine months. The course of the manifest disease itself is extremely variable with regard to severity of symptoms, type of prevailing lesions, acute attacks, remissions, complications and final outcome. In spite of all variations and transitions three definite clinical types stand out:

*Leprosy lepromatosa* (tuberculous, cutaneous leprosy, L type)

*Leprosy nervosa* (anesthetic, neural leprosy, N type)

*Leprosy mixta* (L plus N type)

*Leprosy maculosa* is not a type but rather a stage which may be encountered in any of the three types. One or the other type is usually predominant in an area, e.g. neural leprosy in China. The general rule that the neural type is more common in the tropics and the lepromatous variety in the temperate climates has many exceptions.

### The Clinical Especially Cutaneous Symptoms of Leprosy

**The Early Stages.** The primary skin lesion is a round, pink, tan, copper-colored or whitish smooth usually single macula of about 1 cm. which grows slowly up to several centimeters in size and may remain stationary over a long time. The surface is glossy and the edge slightly raised. Later when the periphery grows the center appears depressed or even atrophic. Frequently there is a depigmented areola. *Depigmentation* more pronounced in the colored skin is often the most noticeable element.<sup>23</sup> Sooner or later nervous signs and symptoms in the affected area start. A period of hyperesthesia or numbness<sup>24</sup> may precede the anesthesia. While the sense of temperature is most often the first to be disturbed, after a short time touch and pain and later the sweat secretion become equally impaired. The primary lesion is rarely an object of medical attention. It is hardly ever seen in the leprosarium in Carville La. (Personal communication to the author). The best observations of initial manifestations were obtained by Rodriguez<sup>22</sup> among the children of lepers in Cullion in the Philippines. The primary lesions may look very trivial especially in the colored skin which becomes easily depigmented after scratches and banal pyogenic infection. However the detection of anesthesia establishes the diagnosis of leprosy. Bacilli are not very numerous in the primary lesions. Rodriguez<sup>24</sup> found that the commonest initial sites were the buttocks, the cheeks, the posterior and lateral surfaces of the thighs and the loins. The experiences of other observers are similar.<sup>25</sup> The primary lesion was never seen on the chest or the abdomen, a frequent site of later lesions.



The primary sore is often found on the *nasal mucosa*. Here it may appear as an ulcer of the anterior septum causing epistaxis which is a well known early symptom. Bacilli may usually be found early in the nasal mucus. Mouth and tonsils are other portals of entry.

Some authors believe that leprosy may develop without a primary lesion. In other cases nervous manifestations may be the first signals of the infection.

Since the primary lesion is frequently inconspicuous and without subjective symptoms the *diagnosis of leprosy is usually made after its generalisation* which occurs through the bloodstream and the lymphatics.



Fig. 132 — Leprosy. Early pigmented and depigmented maculae. (Courtesy U. S. Marine Hospital, Cavite, La.)

The following types of lesions, any of which may be noticed first, represent the most characteristic elements of *early generalised leprosy*.

1. *Erythematous maculae* of bluish or pinkish hue which in their early stages fade on pressure. The red spots start as small round lesions of less than 1 cm. in diameter but they grow, multiply, coalesce and form gyrate patterns. The later appearing lesions grow quickly. The individual lesion may disappear without any sequelae or may leave the skin pigmented or depigmented. Depigmented areolae and shift of pigmentation make them resemble primary lesions especially when greater activity causes infiltration. The red spots are found on the face, on the ears, buttocks, the extensor surfaces of the extremities and sometimes on the back. A fine dusty desquamation may be seen on the early maculae.<sup>167</sup>

2. *Pigmented maculae* which may be primary or develop from erythematous maculae. At first they look like freckles or chloasma; later they may grow to

<sup>167</sup>Chikyu and Velasco P. Leprosy. Mon. de Bull. Philippine Health Serv. 21: 5-7, 1971.

hand size. Their distribution is that of the red spots. Sometimes they form gyrate or variegated patterns. There is neither infiltration nor desquamation. In their usually extremely chronic course they lead to nervous leprosy.

3 *Depigmented maculae* (White spots) which have no or only slightly infiltrated edges. They are not completely devoid of pigment but relatively light, especially in the colored skin. The earliest white spots are perifollicular with slight follicular keratosis. They are 1 to 10 cm. in diameter sometimes numerous and arranged in large network like patterns, thus resembling tinea versicolor or vitiligo. Vitiligo however has more distinct borders and the depigmentation is more pronounced. Sooner or later anesthesia, loss of hair, anidrosis and other symptoms of nervous leprosy become manifest. The lesions may acquire an infiltrated active margin. Sometimes they become the site of vesicles or bullae. They may heal with scars.

4 *Local swellings, infiltrations and nodules* in early leprosy are often first noticed on the alae nasi, the ear lobes, the elbows and the knees. They usually develop in or close to the red spots and may become large plaques. They may be few in number or abundant. The cutaneous nodules vary from pinhead to walnut size. At first the surface is greasy and smooth, later dry and scaly, resembling psoriasis. They often appear in crops accompanied by fever and other general symptoms. They grow fast but their growth may become arrested in any stage and there may be no change for years. New nodules may appear around the old ones which may heal with a scar. Some nodules or deep painful ulcers especially under unsanitary conditions occur on the exposed areas of the skin. The ulcers may destroy tendons and muscle and the scars may lead to serious contractures and deformities and to strictures of the upper air passages.

Anesthesia at first only for heat and pain, later for touch is common in the nodules. The bacilli are numerous.

5 *Blisters* and bullae of all sizes may appear on white or red macules or on the normal skin and may form torpid ulcers. The blisters are rare as early symptoms. Early microvascular eruptions which microscopically proved to be lepra were seen in the Philippines in 16 of 40 children.<sup>107</sup>

6 *Nervous disorders* especially disturbances of sensitivity may occur early and are not restricted to the visible lesions. Numbness, a leather glove feeling, itching and other paresthesias especially along the extremities, may become very annoying.<sup>108</sup> *Hyperesthesia* may make the patients move slowly to avoid any touch. They may be unable to turn a key because the pressure of the key against the fingers causes severe pain. This phenomenon has been called the sign of the key by a leprosy doctor who discovered it in himself.

*Pain on percussion* of the bones, especially the clavicles, the olecranon and the skull is often early and pronounced. The deep structures of the foot may be very painful on extension of the ankle joint.

*Anesthesia* a most important sign may develop in connection with visible lesions or independently in apparently normal skin. Rodriguez<sup>109</sup> found leprosy anesthesia fickle and variable and he failed to find anesthesia in cutaneous lesions in 16 per cent of the cases. The legs, dorsa of the feet, forearms, hands and

fingers in the order named are the most frequent sites of anesthesia. <sup>100</sup> Frazier<sup>101</sup> emphasizes the peculiar dissociation of the elements of sensation. The perception of temperature disappears first. Then follows anesthesia for pain and finally for touch. <sup>102</sup> Anesthesia of the little finger especially of the left little finger has often been mentioned as an early symptom. Early anesthetic areas are often found on the ulnar aspects of the forearms and hands and on the lateral surfaces of the lower legs and feet. The nervous disorder may appear on all kinds of macules and trophic ulcers may develop in all anesthetic areas. The superficial nerves most often the ulnar nerve the peroneal and the auricularis magnus may early become thickened and palpable. Atrophy of the musculus interossei and of the hypothenar eminences are further early nervous symptoms.

7 *Anhidrosis* especially of the finger tips is an early symptom and may precede anesthesia. Some disturbance of the sweat secretion can be demonstrated in 70 per cent of the cases (Degotte after Fellner<sup>103 104</sup>).

8 *Discoloration of the skin* The skin often becomes gray or brownish. This is especially conspicuous in the white race. The colored skin has a tendency to become lighter. The skin sometimes takes on a senile and wrinkled appearance.

9 *General symptoms* Chills fever anemia nausea weakness muscular pains, and other general symptoms of bacteremia and toxemia are very common. The fever may be accompanied by profuse sweating during which the patient may notice that parts of his body remain dry.

**Lepromatous Leprosy**—In the lepromatous form the maculae show an early tendency to become infiltrated or nodular. Nodules may appear in varying numbers and sizes often on apparently normal skin without any inflammatory halo. The first stage may look like an acne papule then the lesion becomes firm shotty raised and glossy often with small telangiectasias. The color is pink in the early stages later purple brown copper or bronze. If regression occurs the epidermis of the lesions may peel. The lepromas are often warmer to the touch than the surrounding area. Hyperesthesia and anesthesia are observed in almost all cases but the time of appearance and the site vary. If cut the patient may feel the touch of the knife but no pain. The lesions may coalesce and form plaques. Such large or small infiltrations may remain stationary for a long time and then resume their growth or undergo regression or ulceration which may partly by secondary infection reach a great depth and width especially in tropical countries. The ulcers may finally heal with scars which reflect the degree of destruction. All stages—infiltration single and coalescent nodules ulceration and scarring—may be encountered in the same patient at the same time so that an exceedingly multifiform picture results. The face is the main site of the nodular changes. The forehead the eyebrow region the nose the chin the lobes of the ears and finally the entire face may become involved. The development of the lepromas on the face is determined by the fibrous and muscular strictures. The fibrous strands crowd the infiltrates together into bulging tumors.

<sup>100</sup>Frazier C N. Leprosy. Epidemiology and Natural History. J A M A 123: 76, 1917.

<sup>101</sup>Fellner M. Leprosy—Review of Literature for 1910. Dermatologica 85: 121-124, 1941.

<sup>102</sup>Fellner M. Leprosy. Dermatologica 86: 122-124, 1939.

and divide them by deep creases. Thus the lion face the *facies leonina* of advanced tuberous leprosy results. Patients in this stage have an amazing similarity. It may be difficult to tell from the face, whether the patient is young or old man or woman or even whether he is colored or white since the colored skin often becomes lighter and the white skin darker. The nose becomes swollen partly by specific involvement of the nasal mucosa which may lead to complete destruction of the septum with subsequent collapse of the nose. It is surprising that the sense of smell remains destruction for a long time. Corresponding lesions appear in the mouth the pharynx and the larynx. There are infiltrations ulcerations and scars with resultant deformations and strictures. The eyes become involved in nine out of ten fully developed cases. The scalp and Scarpa's triangle often remain free and the trunk generally is not as heavily involved as the face. The buttocks are common sites of large nodular plaques.



FIG. 133.—Leprosy on leprosy. (Courtesy Division of Dermatology Department of Medicine University of Chicago.)

Involvement of the *lymphatics* causes elephantastic changes, especially of the lower legs with all the complications of the syndrome such as recurrent erysipels and fever ulcerations and finally mutilations. The external genitalia are commonly affected. Every internal organ may take part in the process though with great variation. In some cases the gastrointestinal symptoms dominate the picture in others respiratory or urinary complications dominate. The disease usually stretches over many years even 2 or 3 decades although acute cases with exanthematic eruptions of lepromas on almost the entire skin

severe prostration of typhoid type and rapid fatal outcome are known. The chronic course is more or less often interrupted by acute febrile episodes, the lepra reactions or *acute attacks* which contrast strangely to the otherwise extremely chronic course. If the reactions are long and relapsing they may precipitate the outbreak of lepromas and aggravate the course. On the other



Fig. 131 — Leprosy. Lepromatous eruption. (Courtesy U. S. Marine Hospital, Carroll, La.)

hand, however, short reactions may exert a healing influence. Urticaria perstans-like lesions of comparatively transitory character have often been seen to appear during the lepra reaction. Existing lesions may become edematous, erysipeloid or vesicular, indicating a severe focal reaction. Remitting fever, arthritic pains and general swelling and tenderness of the lymph nodes may accompany the reaction. The sedimentation rate is increased. The lepromin reaction (see below) is negative.



Fig 135 —Leprosy papular exanthema. (Courtesy U S Marine Hospital Carroll Le.)



Fig 136 Leprosy Leprosoma Courtesy Dr E R Kollerberg

J. Jadassohn<sup>98</sup> was the first to interpret the lepra reaction as a phenomenon of allergy to the leprosy bacillus. This opinion is today widely accepted.<sup>99</sup> Between the attacks periods of relative well being and regression of the lepromas may set in making the patients hopeful and believing that they are on the road to recovery. This hope is however too often deceptive. Suddenly fever heralds



Fig. 137 — Advanced lepromatous leprosy (Courtesy U. S. Marine Hospital, Carlisle, La.)

a new outbreak, with the appearance of new or the enlargement of old nodules. If the patient lives long enough the healing tendency becomes more pronounced and gradual transition into atrophy and scarring may reach an *arrested state* which amounts to healing. Actual spontaneous and relatively sudden healing with regression of all lepromas occurs occasionally. In such favorable cases the bacilli disappear from the nose and after long observation such a patient may be considered healed according to our present knowledge. The neural form is more likely to become arrested than the lepromatous variety, but arrest or healing is the exception in both types. Ordinarily the patient is condemned to a long period of increasing suffering. The involvement of the air passages and the eyes, the loss of voice, the general induration and infiltration of the skin, the nervous disturbances, the pain, the effort connected with the slightest movement, the terrific odor, diarrhea, and many other afflictions, among which the mental suffering of being an outcast is not the least, must make death appear as a salvation. Pulmonary tuberculosis is a frequent complication and cause of death in advanced lepromatous leprosy.

<sup>98</sup> Pardo-Castello, V., and Tian, P. H. Leprosy: Correlation of Its Clinical, Pathologic, Immunologic and Bacteriologic Aspects. J. A. M. A. 121: 1205-1209, 1942.

**Neural Leprosy** —*Leprosy nervosa* generally takes on a still more chronic course than the tuberculous form. Cases of 60 years duration are on record and long periods of apparent arrest may occur.

Fever and other general prodromes herald the cutaneous eruptions more frequently than in tuberculous leprosy.



Fig. 128. Neural leprosy. (Courtesy Dr. John A. McCall, Department of Medicine, University of Chicago.)

In the early stages the appearance of all three types of maculae, the red spots, the pigmented spot, and the white spots, dominates the picture, with a conspicuous absence of infiltrations and nodules. The distribution is usually fairly symmetric but varying in size and shape. Symmetric erythema nodosum-like eruptions occur. The spots become anesthetic within a few days. Blisters are common and may predominate so that a pemphigus-like picture results. However, Nikolsky's sign is negative. The bullae may increase peripherally, surrounded by an inflammatory vesicular areola. Large bullae may form destructive foul ulcers which heal slowly. The ulcers are painless. In some cases no actual bullae develop, but the epidermis forms a dry, scaly crust of yellowish-brown color. The predominantly bullous and ulcerative type of



leprosy is called *lazarine leprosy*. The content of the blisters contains many bacilli but the tissues are able to destroy them quickly so that they cannot be found in sections. The lepromin reaction is positive indicating good defense. The prognosis is relatively good.<sup>101</sup>

Paresthesias, hyperesthesia and anesthesia are the common complaints of beginning neuritis; muscular atrophy, paralysis and trophic ulcers follow later. Some of the nervous complications which predominate in *lepra nervosa* have already been described.



Fig. 130 —Lazarine leprosy. (Courtesy U. S. Marine Hospital, Carville, La.)

The affected nerves often become thick, spindle or rosary like so that they can be palpated. Sometimes only a relatively small area of the skin becomes anesthetic, and the whole process may become arrested at this stage and stay so for a long time with no other symptoms until new similar crops continue the development.

Anesthesia, the most characteristic phenomenon of nervous leprosy, leads to ulcers and to mutilation. The feet, lower legs, hands and forearms are most commonly affected. Beginning at the little finger the anesthesia may involve the whole arm; in similar fashion a leg may become anesthetic. Later on symmetry is pronounced. It must be stressed that anesthetic areas are not sharply bordered and that they do not exactly correspond to the nerve supply.

The successive impairment of the senses of heat, cold, pain, touch and pressure has been mentioned earlier. Deep muscular and joint perception remains intact. The mucosal surfaces may become anesthetic too. The scalp is seldom involved.

Muscular atrophy usually starts in the small muscles of the hands, leading to a clawlike contracted hand which can hardly be moved. Similar sequelae develop in the feet. After an initial increase the reflexes disappear. Neuralgic pains in the trigeminal area are common. While total paralysis of the facial nerve is rare, the muscles which close the eyes are frequently paralyzed. Lagophthalmus, ectropium, loss of eyelashes and dryness of the conjunctivae finally lead

to the characteristic *rotunditas oculorum* which since the middle ages has been known to be characteristic of the leper. The empty stare of such eyes, together with partial or total immobility of the face, creates the typical *facies antonina*.

The skin as already mentioned generally becomes wrinkled ashen or pigmented. Gradually the sebaceous glands disappear. The nails may partially or totally atrophy and disappear.



Fig. 40. Leprosy. Malakia. Courtesy U. S. Marine Hospital, Carroll, La.

*Mutilations* follow *anesthesia*. The destructive process may start with an abscess or trophic ulcer. Resorption of bones especially of the fingers may be a factor. The middle phalanx may disappear first so that by contraction the first and third phalanges become drawn together. Ainhum like strangulations are another feature. All the processes *anesthesia*, muscular atrophy, trophic ulcers, bone resorptions, secondary infection and gangrene may finally lead to the complete loss of fingers, toes, hands, feet and even whole extremities.

It is not surprising that mutilation and all the other sequels of the nervous involvement finally lead to *cachexia*. It is however most amazing that life

frequently continues for long years in spite of such destruction and suffering in which the body is dead before the patient dies (Danielssen after Klingmüller)<sup>342</sup>

*Lepra mixta* combines features of both types. It is in some regions more common than the tuberculous or nervous forms.

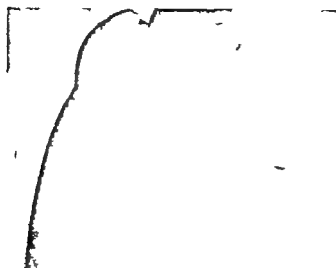


Fig. 141.—Leprosy 31 Baiton. (Courtesy Dr. E. R. Kellerberger.)

**Tuberculoid Leprosy (J. Jadassohn<sup>343</sup>)**—Besides the lesions of lepromatous and neural leprosy one may encounter round or gyrate flat smooth slightly discolored skin lesions which may be large or small. The center is usually depressed and the edge slightly raised. Often especially in the edge small lupoid soft nodules can be demonstrated which under the pressure of glass leave a yellowish spot. These show little resistance to piercing with a bulbous probe. Anesthesia is not very marked but some authors found tuberculoid lesions very frequently in the neural type (Lowe et al. after Wilcocks<sup>344</sup>; Ota and Sato after Klingmüller<sup>345</sup>). Some of these cases have sarcoidal features.<sup>346</sup> It seems to be quite certain that tuberculoid leprosy does not occur together with lepromas,<sup>347</sup> at least this combination must be very rare. Tuberculoid leprosy is of greater theoretical than clinical importance because its tuberculoid structure and paucity of bacilli demonstrate the so-called law of J. Jadassohn and Lewandowsky according to which tuberculoid structures are apt to appear where microorganisms or their products are destroyed by the local immune-biologic reactions (see page 180). In other words the immune-biologic defenses in tuberculoid leprosy are excellent which is in line with its relatively benign course (see also lepromin reaction).

These cases are generally rare though quite frequent in some small localities. They are more often seen in the Negro<sup>348</sup>

<sup>342</sup>Kellerberger<sup>342</sup> revised formulation: its evolution of the word rapidly since relatively slow destruction seems likely produce berculoid structures.

<sup>343</sup>Wilcocks C: Summary of Recent Abstract (Leprosy) Trop. Dis. Bull. 60: 409-415, 1913.

<sup>344</sup>Bagatier W: Allergic Reactions I. Tuberculoid Leprosy. Rev. Wehner 19: 299-303, 1910.

*Mucosal Manifestations —*

The mucosae of the upper air passages are in almost all cases involved though in widely varying degree.<sup>264</sup> The nose though rarely affected in neural leprosy has been found involved in the lepromatous variety in 33 to 96 per cent according to a great number of authors from many countries. The nasal mucosa is often the first site of lepromatous lesions and bacilli can often be found in the



FIG. 113. Tuberculoid leprosy. (Courtesy U. S. Marine Hospital, Carroll, La.)

nasal discharge when no other symptoms exist. The vestibule which may be filled with crusts which have formed over ulcerating lepromas in the nasal mucosa proper is often the site of the same sequence of changes which takes place on the skin. I.e. inflammation infiltration ulceration and scarring. The infiltrates appear as tough yellowish-pink pinhead to cherry stone sized granulations which soften and ulcerate quicker than the corresponding skin lesions. The place to look for the lesions is the cartilaginous septum the vestibule and the lower turbinates. Perforation of the nasal septum occurs in about 40 per cent of all types.

Oral infiltrations consisting of grouped small yellowish pink nodules are often found on the *palate*. The pharyngeal reflex is lacking in 60 per cent

<sup>264</sup>Plakerton, F. J. Leprosy of Upper Respiratory Tract. *Trans. Laryng. Otol. & Rhin. A. S. A.* Vol. 57, 118, 1937.

of the neural cases (Belowdon after Klingmüller<sup>10</sup>) Scarring results in deviations of the uvula. The guma, the tonsilla and the labial mucosa are less often involved. The lips become more often affected in the skin and vermillion parts than in the mucosa proper.



Fig 102 — Leprosy. Lepromas of the palate. (Courtesy U. S. Marine Hospital, (arrived 1A.)

On the *tongue* lepromatous lesions occur as flat yellowish or silvery glossy or tendinous discoid polygonal or streaky nodules or as diffuse infiltrations of the base of the tongue. Generally the tongue resists the lepromatous involvement longer than other parts of the mouth. The incidence of leprosy of the tongue given in various statistics from different countries varies from 5 to 50 per cent. The same type of conglomerations of yellowish pink granulations as are found in the oral cavity occurs on the epiglottis and in the arytenoid area while the vocal cord usually resists for a long time. The trachea is rarely affected and if so in the uppermost part.

The *lungs* may become lepromatous but this is relatively rare.

The *eye* is very often affected in Norway in almost 100 per cent of the lepromatous and in 60 per cent of the neural cases. The percentages of other countries are smaller but still considerable. Lepromatous involvement of the lids madarosis specific conjunctivitis ectropion keratitis iritis episcleal lepromas lagophthalmus and its sequelae muscular disorders atrophiam bulbi and many other lesions are well known.<sup>101</sup>

The *auricle* especially the earlobe is a common site of lepromas while the ear duct usually stays free. The internal ear is hardly ever affected.

The *sebaceous glands* seem to be more active so that the skin over the lepromas is other than normal. On this phenomenon was based the medieval 'water test'. If the skin did not become wet from water the patient was assumed to be a leper.

*Perspiration* may within the affected areas be increased in the early stages and then paralyzed. The loss of perspiration may be due to specific destruction of the sweat glands or to nervous disturbance.

The *hair* of the body and the beard may early become dry brittle and thin. The early loss of the lateral third of the eyebrows has often been emphasized. The hair of the head is as a rule surprisingly resistant even in advanced cases, but is lost in the affected areas.

Heller<sup>22</sup> in his monograph on the diseases of the *nails* reports thinning longitudinal grooves and shedding. Occasionally the nails withstand the advance of the disease surprisingly well so that normal nails can be seen on severely affected fingers of mutilated hands. Complete and permanent loss, or reduction of the nails to tiny horny cones are characteristic of the terminal stages.

**Pathological Histology**—There are three types of pathological changes caused by the leprosy bacillus: the infective granuloma, the nonspecific inflammation and the tuberculoid structures (Lewandowsky after Klingmüller).<sup>23</sup> Furthermore the Hansen bacillus may be found in tissues without causing any changes. The *lepromatous* changes start most often in the walls of the vascular plexus surrounding the follicles, the arrectores pilorum, the sweat glands, the central vessels of the papillae and the cutaneous nerves. These early localizations are indicative of a hematogenous infection. The infective granuloma consists of lymphocytes, plasma cells, epithelioid cells and giant cells. Usually the lepromas contain great numbers of bacilli arranged in bundles or loose groups between the cells. In the capillaries of the papillae in the lymphatics and in round dense intracellular conglomerations in the cells which are known as globi. Globi often contain more bacillary granula than rods and may become large enough to be macroscopically visible. The intracellular bacilli are mostly found in the lepra cells which are large polynuclear cells with a foamy protoplasm. The lepra cells stem from histiocytes and as such they are part of the reticulo-endothelial system. Their protoplasm is rich in lipids. Before the leproma invades the epidermis, it stays for a certain period separated from it by a characteristic leprosy free layer of tissue, a phenomenon which A. Neisser had observed.

*Neural leprosy* is characterized by interstitial neuritis. Absence of granuloma formation is striking. The histology of *tuberculoid leprosy* resembles that of Boeck sarcoid. The lesions consist of sharply bordered perivascular granulomas, sometimes with a necrotic caseating center. Plasma cells are scarce, epithelioid cells abundant. Giant cells of the Langhans type complete the tuberculoid picture. Frazer<sup>24</sup> says that the most typical tubercles of the skin are found not in tuberculosis but in leprosy.

The invasion of the nerves may be metastatic and hematogenous or contiguous from the skin. The latter is very common and explains the predominance of very peripheral neural changes in sensory nerves over motor paralyases.

**Test and Diagnosis.**—Allergic and serologic reactions have not become as important in the diagnosis of leprosy as in other diseases. In advanced cases the Wassermann and Kahn reactions are often positive. While many

believe that these are nonspecific reactions some more recent investigators (Cundersen Ole Berner after Fellner<sup>98a 98b</sup>) believe that a positive Wassermann in a leper means syphilis

*Rubino's*<sup>98c</sup> reaction based on the sedimentation and agglutination of prepared mutton erythrocytes with the test serum is negative in nonlepers<sup>98c-98d</sup> often positive in lepers especially in the tuberculous form

Some lepers react to *tuberculin* probably without being tuberculous. The serum of nontuberculous lepers may give a positive complement fixation test for tuberculosis. These occasional difficulties are further increased by the frequent tuberculous infection of advanced lepers<sup>98e 98f</sup> (Babes after J. Jadassohn<sup>98g</sup>)

The serum of lepers is highly toxic to growing young plants<sup>99</sup> in contrast to the serum of patients with syphilis or tuberculosis.

Allergic skin reactions with allergens derived from *lepromas* have become important.<sup>97i 97j</sup> Silent immunization in leprosy surroundings and anergy must be considered in the interpretation

The *Mitsuda*<sup>97i</sup> reaction is not so much used to establish the diagnosis of leprosy as to test the immune-biologic defense of a patient in order to gain a basis for prognosis. The test consists of the intracutaneous injection of 0.1 c.c. of lepromin, an extract from lepromas<sup>98</sup>. If the reaction is positive a papule develops in the second week. It reaches its acme in the fourth week with a nodule  $\frac{1}{2}$  — 1 cm. in diameter which eventually may ulcerate and slowly heal. The papule has a tuberculous structure. The test is often positive in healthy persons from leprosy surroundings and in tuberculous leprosy it is often negative in lepromatous leprosy and doubtful in cases with histologically nonspecific inflammatory lesions. The negative lepromin reaction in lepromatous leprosy with abundant bacilli is explained by a lack of defense to the infection and is therefore considered a bad prognostic sign. The positive reaction is considered as an indication of vigorous defense and relatively favorable prognosis (see tuberculous leprosy and law of Jadassohn and Lewandowski pp. 180 and 242)

Febrile and focal reactions to 0.2 to 3.0 grams of *potassium iodide* or to intravenous injections of sodium iodide occur frequently in lepers and have diagnostic value. The serologic reactions may become activated and the increased nasal secretion may lead to the detection of leprosy bacilli in smears

<sup>98</sup>Rubino M. O. Séro-diagnostic de la lèpre par l'agglutino-sédimentation des globules rouges de mouton formolés. Bull. Acad. de méd. Paris 196 890-902 1931 also Ann. Inst. Pasteur 67 147 172 1931

<sup>98b</sup>Lépine P. Markianos, and Papayannou, A. Valeur pratique de la réaction de Rubino pour le sérodiagnostic de la lèpre. Bull. Soc. path. exot. 28 842 1932 Ekl. 43 402.

<sup>98c</sup>Hombria M. Zum serologischen Studium der Lepra. Acta dermo-iff. 28 183-200 1932 Ekl. 44 635

<sup>98d</sup>Montañes, P. Diagnostischer Wert der Rubino-schen Reaktion bei Lepra. Acta dermo-iff. 26 241-263 1932 Ekl. 44 840

<sup>98e</sup>Branta, J. Erythrocytenagglutinationsreaktion bei Lepra. Lat. anat. Kurs 11 617-623 1932 Ekl. 44 23 1933

<sup>98f</sup>Jacki, D. J. Phytopharmacologic studies on the sera of Pseudophaga, Syphilis, and Leprosy. Acta dermo-iff. 28 126-137 1932

<sup>98g</sup>Mitsuda, K. Trousseau conférence la semaine de la lèpre. Communications et débats Paris 1924 J. U. Méd. 1924 et fil.

<sup>99</sup>Harvey P. pathische Hautreaktionen bei Lepra. Zische f. Immunitätsforsch. exper. Therap. 47 375-381 1926

which were previously negative. Biopsy of the skin or nasal mucosa, testing of the serum of blisters produced by carbon-dioxide snow and puncture of lymphatic nodes are some of the laboratory methods successfully used to find bacilli. For the preparation of nasal smears the mucosa should be gently scraped without causing bleeding.

Clinical similarity to a great number of dermatoses may develop in one or the other stages of this chronic disease: Psoriasis, ichthyosis, mycosis fungoides, leukemia, blastomycosis, syphilis, lupus erythematosus, vitiligo and a number of other skin diseases may occasionally be suggested by atypical leprosy.

The course, the occurrence of leprosy in the surrounding region, macules and lepromas, biopsy, and above all anesthesia will usually decide the question. If the cooperation of the patient in testing of the sensory functions is lacking, the *histamine test* may prove valuable. The skin is pricked with a needle through a drop of histamine salt solution 1 — 1000. In paralysis of the sensitive nerve endings a wheal appears as in the normal skin, but it lacks the red areola which is normally seen. This is called a negative histamine test. Pardo-Castello and Tiant<sup>62</sup> found this test negative in the cutaneous lesions of leprosy. The most difficult problems, however, may arise from nervous diseases and particularly from syringomyelia. Here the anesthesia is more sharply bordered and the muscular atrophy (which in leprosy is usually restricted to the anesthetic parts of the hands) affects the arms and shoulders. Scoliosis, bulbar symptoms, pathological fractures of the long bones, ataxia, central unilateral facial paralysis, tremor, spasms—in short, central neurologic symptoms and signs—are more suggestive of syringomyelia. The neural phenomena of leprosy are usually of peripheral character.

**Treatment**—No specific therapy is known. The derivatives of the chaunmoogra oils which are obtained from several tropical trees are so far the most effective drugs. Recently promin, a sulfone derivative, has given encouraging results.<sup>63</sup>

<sup>62</sup>FACET, O. H., POTTER, R., JOHNSON, F. A., DINEEN, J. P., FREEMAN, R. N. and KERRIE, C. O. Promin Treats Men of Leprosy. Pub. Health Rep. 58: 729-741, 1943.



## CHAPTER XIII

### DERMADROMES OF INTOXICATIONS

A poison may cause a dermatosis by external contact without systemic interference (discolorations by dyes necroses by caustics) or by damaging the skin as part of the damage to the entire system. In the latter case one must separate the intoxications in the strict sense from the allergic reactions. In *intoxications* the causative agent is toxic to all individuals if it is absorbed in a certain dose the damage it produces depends on the nature the amount and concentration of the poison and also on the length of time it acts excessive doses being lethal. The poison can be excreted and antidotes may reverse the process. There is no incubation period and the agent may be found in the tissues by chemical analysis. These are some of the features characterizing intoxication in contrast to allergy (Tzanck after R. L. Mayer<sup>171</sup>)

Thallium alopecia and argyria are examples of this, sometimes called classical type of toxidermia.

In the case of *allergic reactions* a specific alteration in the capacity to react acquired by previous exposure to the agent<sup>172</sup> is the dominant pathogenetic factor though the nature and dose of the poison (allergen) should not be underrated. The allergic dermatoses have been the subject of several recent monographs<sup>173-75</sup> and their character as a manifestation of internal disorders is not yet clearly enough understood to warrant more than a short mention in this book. The dermatoses caused by metabolic and bacterial toxins are being dealt with in other chapters. Thus only the *skin manifestations of systemic poisonings* in the strict sense of the term shall be discussed in the following chapter.

#### Arsenicals

Arsenical poisoning occurs in a great variety of circumstances. It is an industrial hazard in the mining and smelting of many ores especially gold and copper. The gases from the copper furnaces, the commercial metal sulfides as well as sulfuric acid are often contaminated with arsenic. Lead arsenite calcium arsenite and Paris green are rat poisons and agricultural insecticides used on such important crops as cotton tobacco apples grapes and vegetables.<sup>177</sup> Several arsenites sulfides of arsenic and other compounds are bright colored pigments which in spite of modern paints and legislation have been and probably still are in occasional use in wall paints wall papers toys and colored papers.

Medical administration of arsenicals is a common cause of arsenicism. Suicidal and homicidal attempts and laboratory and industrial accidents are

<sup>171</sup>Mayer R. L. *Toxicodermatosen* Handb. d. H. Gk. 4 2 1252, 1923

<sup>172</sup>Kelshberger S. B. *Derivation of Allergy* Springfield, ID 1940 (Charles C. Thomas)

<sup>173</sup>Tzanck E. *Allergy* New York, 1934 Grune & Stratton

<sup>174</sup>Ajres R. J. and Anderson, W. F. *Cutaneous Manifestations of Arsenic Poisoning* Arch. Dermat. & Syph. 30 33-43 1924

relatively rare by comparison. Mass poisonings affecting many thousands of people and remaining unexplained for a long time have occurred in a great number of instances. Such a so-called epidemic terrified Paris in the 1830's. About 40 000 persons became victims of a disease then called acrodynia which later was identified as arsenic poisoning. In later epidemics the cause was established by means of modern chemistry. There were several mass poisonings by wine from vineyards where arsenicals had been used for spraying. The last one occurred on ocean liners in 1932<sup>97</sup> <sup>98</sup>

In 1900 sulfuric acid containing arsenic, used in converting cane sugar into invert sugar for beer brewing in England, caused one of the greatest mass poisonings in history. Drinking water contains arsenic in toxic amounts (more than 0.2 mg. per 1000 c.c.) in many localities (Kathe after R. L. Mayer<sup>99</sup>). Chronic skin manifestations are likely to be found among the inhabitants as was shown in the description of the drinking water epidemic in the little Silesian mining town of Reichenstein.

The descriptions of these epidemics (partly given by such masters of dermatology as Vidal Barthélemy and A. Neisser and their schools) laid the foundations of our present knowledge of arsenical intoxication which is one of the best studied of all human poisonings.

Acute arsenical poisoning is characterized by severe gastrointestinal symptoms which resemble cholera and may cause death in a short time often after a few hours. Excessive lacrimation and salivation are early manifestations.

Within a few days or a week polyneuritis with multiple paralyses may develop together with cutaneous symptoms and may last a long time. Formication pruritus numbness, wrist drop and tabes-like syndromes are characteristic neurologic symptoms. There exist a great variety of clinical pictures, e.g. psychoses and agranulocytosis, but nervous and cutaneous symptoms are significant if not the dominating features of the subacute and chronic cases.

The diagnosis of arsenic poisoning<sup>977</sup> depends on the history, clinical appearance and the presence of arsenic in the urine or hair in an amount which is decidedly above or a multiple of the value which may occur under normal conditions. Geographic location, drinking water peculiarities of the soil or a diet rich in seafood which may contain as much as 8 mg. per kilogram are factors which must be considered. Representative normal figures have been stated as 9.7 mg. per hundred grams substance for the hair and skin, 17.2 mg. for the nails and 10.4 mg. for the urine<sup>980</sup>. Wilcox<sup>981</sup> and Ayres and Anderson<sup>977</sup> recommend the Guthzeit test for urinary analysis which is a relatively simple color test.<sup>982</sup>

<sup>97</sup>Thorel and Viennet. A propos d'une intoxication collective par l'arsenic, Ann. de dermat. et syph. 8: 814-821, 1932.

<sup>98</sup>Mölkens. Ueber eine Massenvergiftung nach Weintrauben an Bord. Deutsch. med. Wochenschr. 1932 I: 844-845.

<sup>99</sup>Reiber O. and Marfurt E. De la courbe normale en arsenic dans le corps humain. Helvet. chim. acta 6: 750-756, 1923.

<sup>977</sup>Wilcox W. Acute Arsenical Poisoning, T. Med. Leg. Soc. Lond. 33: 6-162, 1930.

<sup>980</sup>A. Loeferlich, W. Detection of Poisons, ed. 4, Philadelphia, 1918, P. Blakiston. See A. C.

Sometimes it is possible to demonstrate arsenic in the biopsy specimen of skin lesions.<sup>182,184</sup> A progressive diminution of arsenic in the urine with clinical improvement under sodium thiosulfate therapy and the recurrence of symptoms on exposure to arsenic would be further proof. A positive patch test would show that there has been enough exposure to arsenic to produce sensitization.

**Dermadromes**—The earliest skin manifestation of arsenical poisoning is *pruritus* which in some cases is restricted to the palms and soles. Conjunctivitis, coryza and *puffiness of the eyelids* are also early warning signals which are observed more often in the course of prolonged arsenical treatment than after acute poisonings with one large dose. Other frequent and early symptoms are dis-



Fig. 144—Exfoliative dermatitis (erythroderma) following arsenic poisoning. (Courtesy Dr. Garrett Cooper.)

tinctly bordered *palmar and plantar erythemas*. Their diagnostic importance is great because of the ease with which they can be noticed in ambulatory patients under continual arsenic treatment. The accumulation in the sweat glands which concentrate and eliminate the arsenic (Hutchinson after Ullman<sup>185</sup>) as well as the arsenophile keratotic epidermis are responsible for the site of the erythemas. *Palmar planta sweating* is known as an early symptom.<sup>186</sup>

<sup>182</sup>Osborne E. D. Microchemical Studies of Arsenic in Arsenic Dermis (U). Arch. Dermat. & Syph. 18: 37, 1936.

<sup>184</sup>Osborne E. D. Microchemical Studies of Arsenic in Arsenical Pigmentations and Keratosis. Arch. Dermat. & Syph. 18: 773-783, 1938.

<sup>185</sup>Ullman K. Ueber Arsenexan home im Hilde als ter wie chronischer Arsenvergiftungen. Kl. Wchnsch. 1831 II: 1805-1808, 1841: 1849, 1931.

<sup>186</sup>Osborne E. D. & P. Skin Manifestations in Arsenic Poisoning. Nederl. Tijdschr. Geneesk. pp. 5267-5269, 1935. Ed. 83: 193.

Widespread or even truly generalized rashes following the intake of arsenicals may be seen together with or following the palmar-plantar erythemas.

*Scarlatiniform morbilliform* and *erysipeloid* erythemas are also known. Of greatest importance are the *eczematoid eruptions* which if further intake of arsenicals is not halted may rapidly develop into generalized exfoliative dermatitis which is such a great hazard in the use of the arspenamines (see there) while it is rarely provoked by the inorganic arsenicals.

Generalized rashes may also be urticarial vesicular or bullous. K. Ullmann<sup>87</sup> emphasizes the sequence of pruritus urticaria and edema followed by circumscribed and later generalized erythemas.

The generalized exanthema may also appear as large or small scaly patches in some instances resembling *psoriasis rosea* or *parapsoriasis*. Older lesions of this kind may have a heavier covering with scales and thus imitate *psoriasis* closely. The arsenical erythema may also surround and accentuate pre-existing psoriatic lesions.<sup>87</sup>

The eruptions sometimes imitate *lichen planus*. This is a remarkable fact with regard to the great efficacy of arsenic in lichen planus. No generally accepted explanation for this clinical coincidence has been offered and cannot be expected before more about the etiology of lichen planus is known.

*Scleroderma*, as a probable arsenical sequel<sup>88 89 90</sup> has been observed in a considerable number of instances. Generalized *postuloderma* as a permanent damage after arsenical dermatitis, is also on the long list of rare arsenical arspenamine reactions.<sup>90</sup> Recently nine cases of *acrodermatitis chronica atrophicans* have been observed in a group of wine growers affected with occupational arsenicism.<sup>91</sup>

*Edema* is a common symptom in arsenical eruptions. There may be only light puffiness of the eyelids and cheeks, but generalized edema is hardly ever absent in the severe forms of dermatitis.

Petechiae and other *hemorrhagic* symptoms are of rather grave prognostic significance.<sup>92</sup> *Herpes zoster* is reported to occur in 18<sup>93</sup> 8<sup>94</sup> or even 10 to 20 per cent<sup>95</sup> of the cases. The high incidence of herpes zoster in the English beer epidemic was one of the facts which pointed to arsenic as the causative factor.

Pustules, ulcers, necroses and perforations of the *nasal septum* are caused by the local external caustic effect of the arsenic.

The *oral mucosa* may participate early in the toxic syndrome with pharyngitis and gingivitis. Ulcerative stomatitis or glossitis may occur in severe cases.

<sup>87</sup>Ullmann K. 'Arsenikarose und Arsenveranbildung, Zbl. 36 341, 1931.

<sup>88</sup>Ayres R. J. Scleroderma. Possible Manifestation of Chronic Arsenic Poisoning. Arch. Dermat. & Syph. 2: 747 1920.

<sup>89</sup>Ayres R. Jr. A Fifth Case of Scleroderma With Arsenic in the Urine. Arch. Dermat. & Syph. 2 315-247 1921.

<sup>90</sup>Cannon A. D. Haroldi Karry M. D. and Flischer J. K. Psoriasislike Changes in Skin, Following Arspenamine Dermal Rx. J. A. M. A. 218: 123-129 1943.

<sup>91</sup>Bruckmaier H. Acrodermatitis chronica atrophicans bei Weinern mit Arsenmarklsgungen. Arch. f. Dermat. 96 379-84 703 939.

<sup>92</sup>Nelson Herpes zoster After Arsenic-Behandlung, Monatsh. f. prakt. Dermat. 21: 302, 1890.

<sup>93</sup>Geyer L. Chron. Hautveränderungen beim Arsenikismus und Betrachtungen über die Miasmenkrankungen in Reichenstein in Schlesien. Arch. f. Dermat. Syph. 43 221, 1899.

The *hair* is almost always diffusely shed. The alopecia is complete in severe cases of arsenical dermatitis.

The *nails* usually record severe dermatitis as well as acute especially single-dose poisonings by cross furrows (Beau's lines) or with white<sup>282</sup> or gray cross lines. The latter have become known as Mees bands<sup>283 284</sup> and are often associated with polyneuritis arsenicoma. They are dull glistening bands extending across the breadth of each finger nail. The bands appear at the lunula about eight weeks after the poisoning. If one adds 10 days for every 1.1 — 1.2 mm of the distance from the proximal border of the lunula to the distal border of a band one can determine the approximate date of the poisoning. The arsenic content of a band has been found to be 10 times higher than in the undiscolored parts of the nails.<sup>285</sup>

The condition is apparently identical or similar to the leukonychia striata which was observed in many instances during the English beer epidemic and in other instances of arsenical poisoning. The nails may be shed after severe arsenical dermatitis.

Arsenical dermatitis of all types heals with *hyperpigmentation* of varying intensity which may even develop without preceding noticeable inflammation.

The distribution, depth and duration of the hyperpigmentation vary within wide limits. The areas which have a natural tendency to darken such as the genitals, groins, umbilicus and mammillae as well as scars, healing skin lesions and pressure and friction points are often highly pigmented.<sup>286</sup>

The individual tendency to pigment has a much greater influence on the melanosis than the size of the doses of arsenic. Melanosis may appear as early as 12 days after the onset of arsenical medication and after small doses. On the other hand severe poisoning may fail to produce it. This is well demonstrated by the fact that in poisoning from drinking water with generally equal supply to the population only some persons develop marked melanosis. The discoloration may start insidiously and reach any even the severest degree.<sup>287</sup>

The diffuse type of arsenical melanosis is so similar to the appearance of Addison's disease that during the great beer epidemic in England most cases were so diagnosed until the autopsies failed to reveal adrenal changes. The covered parts of the skin seem to darken more than the open ones<sup>288</sup> although the face is frequently affected. In a minority of the cases a dense regularly reticulated or dappled pattern of pigmentation and depigmentation may cover wide areas especially the back. This type of arsenical melanosis has been called *raindrop pigmentation* because of its resemblance to a window pane covered with raindrops. This characteristic type of arsenical pigmentation is often found in chronic arsenicism due to drinking water or prolonged administration of inorganic arsenicals.

<sup>282</sup>Mees, R. A. Een crachtfowl bij polyneuritis arsenicoma, Nederl. Hlschr. Geneesk. 1919 1: 361-366.

<sup>283</sup>Barker, L. F. Exfolia in Dermatitis in Accidental As-Poisoning. Mees Band 1: 101 & 102. Rev. 44: 423-427, 1943.

<sup>284</sup>Wigand, R. Das Mees'sche Nagelband bei Polyneuritis arsenicoma, München med. Wchnsch. 87: 423-424, 1940.

<sup>285</sup>Thorne, B. Arsenical Pigmentation. Arch. Derm. & Syph. 20: 479, 1931.



Fig 143. Arsenical melanosis raindrop appearance. (Courtesy Division of Dermatology Department of Medicine University of Chicago.)



Fig 144 — Arsenical melanosis "raindrop" appearance.

Arsenical melanosis has also been seen to follow the pattern of underlying large veins<sup>77a</sup>

The *depigmenting* tendency after arsenical dermatitis is best observed in Negroes<sup>77b</sup>

In rare instances the *oral mucosa* participates in the pigmentation although the lack of oral pigmentation has often been emphasized as a differential criterion against Addison's disease. The arsenical melanosis may vanish rapidly with the other symptoms of the intoxication but more often it persists much longer or even permanently

The arsenical pigment is *melanin*<sup>78</sup> and as such is iron free. It can be distinguished from arsenic crystals<sup>79a</sup> which lie mostly between the cells.



Fig. 147 — Arsenical keratosis of palms after indeterminate use of Fowler's solution in psoriasis

*Keratosis* are the most common and characteristic and the most easily detectable of all skin manifestations of chronic arsenic poisoning

The keratosis may appear within a few weeks after the start of arsenic intake or as late as many years after the medication or other exposure has been stopped<sup>80</sup>. An erythema may or may not precede their appearance

The characteristic sites of the hyperkeratosis are the palms and soles with their peculiar affinity for arsenic. The areas of friction and pressure which normally tend to callus formation are especially apt to develop arsenical hyper-

<sup>77a</sup>Cannon A. B. and Karelitz, M. B. Vitelline From Arsenicalline Dermatitis And From Arsenic Arch. Derm. & Syph. 28: 642-644 1933

<sup>77b</sup>Gane O. Histologie der Arsenicalline Derm. Beitr. pa. b. Anat. allg. Path. 90: 225-24, 1915

<sup>78</sup>Montgomery H. Arsenic as an Etiologic Agent in Certain Types of Epithelioma, Arch. Derm. & Syph. 21: 218-220 1915

keratoses. Thus the plantar arch and the center of the palms remain relatively free from circumscribed lesions but they are not immune against diffuse keratosis. Occasionally circumscribed keratoses may appear on the back on the chest on the extensor surfaces of the elbows and knees, on the heels, or on the dorsa of the hands and feet <sup>1994-1995</sup>

Hyperkeratoses may be diffuse and cover the entire palms and soles. Much more characteristic, however are the circumscribed lesions. They are often called warts but they are less circumscribed and vascular than ordinary warts. They are cornlike accumulations of horny tissue and because of their completely epidermal structure they are more transparent than warts or corns. Their color is usually pale yellow but thicker layers may take on a dirty gray or even slate or brown hue. The opening of a sweat gland is sometimes visible at the top of a small lesion. The size varies from that of a millet seed to a pea or even an almond. *Hyperidrosis* is a frequent annoying accompaniment which may even be the presenting symptom in cases of arsenical keratosis.



Fig. 4. Transition of arsenical keratosis to cancer.

There exists only a very rough parallel between the appearance of the keratoses and the dose and length of time of arsenical exposure. Examples of extensive keratoses after small amount of arsenic and complete lack of keratoses after huge doses are well known <sup>1996</sup>

Chronic intoxication with inorganic arsenical is especially apt to cause keratoses while they are rarely seen among the tremendous numbers of people treated with arphenamines. The circumscribed keratoses usually disappear

<sup>1994</sup>Kaiser, L. Mächtige papillomatöse Wucherungen auf ekzematöser Haut, *Zbl. B.* 840, 1924



## PLATE II

- 1 Lupus erythematosus acutus. Rapidly fatal case.
- 2 Arsenical keratosis with carcinoma
- 3 Aneurysm of the abdominal aorta. Giant ecchymoses.
- 4 Hypertension. Chronic nephritis. Pruriginous eruption
- 5 "Gabond's skin"
- 6 Erythema palmare (Mitral insufficiency)



PLATE II



gradually with the elimination of the arsenic. Sometimes however they are permanent. If they are removed they grow back rapidly. Such keratoses of many years standing are *precancerous* lesions.

Montgomery<sup>100</sup> saw *epitheliomas* develop in 20 per cent of his 85 cases of arsenical keratosis but the percentage is likely to be smaller in less preselected material than is encountered at the Mayo Clinic.

The cancers are usually of the squamous cell type. Some assume features of Bowen's disease by the formation of grouped or circinate lenticular crusty or scaly papules. But it has not been sufficiently proved that Bowen's disease and superficial epitheliomatosis generally are due to arsenic as had been suggested.<sup>101</sup> Arsenical epitheliomas may also appear independently of keratosis. They may occasionally look like superficial epitheliomatosis forming thin scaly plaques which however often lack the thin threadlike pearly border of this variety of skin cancer.<sup>102</sup>



Fig. 49 — Arsenical keratosis resembling Bowen's disease

Basal cell epithelioma is very rare. The degree of malignancy is relatively low metastases occurring very late. Arsenical cancers of the urethra bladder and bronchi have been observed in rare instances.<sup>103</sup>

The cancers are not very malignant. They metastasize late and are seldom and only after a long time destructive. They respond well to radiation and even the excision of relatively large cancers may be successful. In all cases of

<sup>100</sup>Anderson, V. P. Bowen. Precancerous Dermatoses, Benign Superficial Epitheliomas, Arch. Dermat. & Syph. 25: 1032, 1932.

<sup>101</sup>Goeckerman, W. H. and Wilhelm, L. F. X. Arsenic as Cause of Cancer of Mucous Membranes, Arch. Dermat. & Syph. 62: 641-64, 1940.



Fig 150 — Large arsenical cancer over Achilles tendon. Indiscriminate use of Fowler's solution against psoriasis

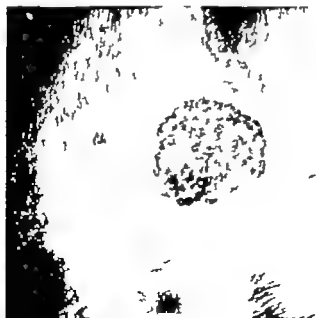


Fig 151 — Superficial epitheliomatosis in patient with arsenical keratosis and history of indiscriminate use of Fowler's solution.



Allergy to arsphenamines in cases of dermatitis has often been demonstrated by positive patch tests.<sup>1006</sup> Women were twice as often affected as men.<sup>1008</sup>

The treatment requires daily injections of 1 gram of sodium thiosulfate and best nursing care. Penicillin is probably helpful in combating pyogenic infection. Liver extract has often been recommended.

Convalescents should not be subjected to any further arsenical treatment.

Early acute arsenical erythema or *erythema of the ninth day* is a febrile multiform rash of unknown etiology occurring in about 3 per cent of the patients treated for the first time with trivalent arsenicals.<sup>1007</sup> The rash is described as generalized and composed of irregularly macular or morbilliform lesions clearing up after 2 days. Arsenical treatment may be continued with extreme caution only but is better replaced by penicillin.<sup>1008</sup>

Other rare eruptions following the use of arsphenamines include *lichen planus* and *lichen spinulosus*.<sup>1009</sup> Jaundice is a frequent after-effect of arsphenamine treatment. There is no consensus whether arsphenamine alone allergy, syphilis, another infection or a combination of factors are responsible for the frequent cases of hepatic disease in the course of antisyphilitic treatment with neoarsphenamine.<sup>1010</sup>

### Gold

Gold poisoning is almost exclusively due to medication, gold-sodium thiosulfate (sancrysin) being the most widely used compound. The general symptoms follow the pattern of other heavy metal intoxications including arsenic. There may be nephritis, enteritis, hepatitis and a depression of the hematopoietic system in severe cases ending in agranulocytosis or aplastic anemia.

Ill effects mostly of a mild nature were estimated to occur in about 10 per cent of 1400 tuberculous patients treated with gold compounds.<sup>1011</sup> They were much more common in the early days of gold therapy when high doses were advocated.

**Dermadromes**—The skin is most often affected.<sup>1012</sup> The injection of a gold salt even in small quantity may cause immediate or early *iritoid reactions* with a flushed face and a sensation of giddiness, sometimes with severe cervical pain. Such reactions occurred most frequently after sodium thiomalate (myochrysin).<sup>1013,1014</sup> They are very rare after gold sodium thiosulfate if it is injected slowly into the vein.

<sup>1006</sup>Schoch, A. H. The Patch Test and the Element of Syringe Contamination in Arsphenamine Sensitization Dermatitis, *J. A. M. A.* 90: 1367, 1933.

<sup>1007</sup>Calhoun, O. and Thomas, E. W. Early Acute Arsenical Erythema, *Arch. Derm. Syph.* 23: 547, 1929.

<sup>1008</sup>Leifer, W. Danger of Continued Arsenotherapy in Cases of Erythema of Ninth Day, *Am. J. M. Sc.* 219: 455, 1945.

<sup>1009</sup>Volavsek, W. Reltene Palvarusarhiden Derma Wehwehr 218: 409-420, 1913.

<sup>1010</sup>Winkler, S. Dermatitis and Icterus Following Arsphenamine and Bismuth Therapy of Syphilis, *Dermatologica* 21: 277-300, 1940.

<sup>1011</sup>Mayer, O. Gold Treatment of Pulmonary Tuberculosis, *Brit. J. Tuberc.* 28: 121-129, 1934.

<sup>1012</sup>Feliner, M. Die Goldtherapie in der Dermatologie, *Skl.* 43: 23, 1912.

<sup>1013</sup>Louis, R. M. Toxic Reactions With Gold Salts in Treatment of Rheumatoid Arthritis, *J. Lab. & Clin. Med.* 28: 1629-1631, 1941.

<sup>1014</sup>Xirakas, J., Lebrun, F. and Mollard, H. Sur quelques accidents (aigus) de la chrysothérapie (une crise ictérique) et de nouvelles localisations éruptions, *Bull. Soc. franc. d. dermat. et syph.* 29: 874-878, 1932.

All the familiar types of toxic exanthems have been observed. Morbilliform and scarlatiniform rashes are relatively common; multiform and bullous eruptions are rare.

Some exanthems resemble pityriasis rosea but they lack the primary lesion.<sup>113</sup> Itching may be the first symptom of all these rashes and should be reason to discontinue the treatment.

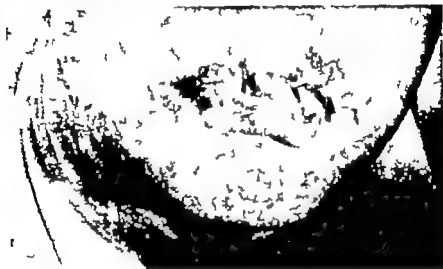


Fig. 152 Acute severe exanthematous eruption provoked by gold therapy of chronic lupus erythematosus

*Hemorrhagic eruptions* seem to occur more frequently than in arsenical poisoning.<sup>114</sup> The tuberculosis or syphilis of the patients treated with gold may have some importance in the pathogenesis of the purpuric<sup>115</sup> mostly petechial rashes. These eruptions are frequently accompanied by other hemorrhagic phenomena especially hematuria. Naturally all hemorrhagic manifestations are potentially serious. *Generalized exfoliative dermatitis* with loss of hair and nails though rarely with a fatal outcome<sup>116</sup> has been observed.<sup>117</sup>

*Lichen planus-like eruptions* seem to be a feature of the gold dermatoses.<sup>118</sup> They may be subacute with violent itching vesicles and blisters or even turn into generalized exfoliative dermatitis. More commonly they consist of relatively

<sup>113</sup>Wheeler J. and Corvillat C. J. Pityriasis-Rosea-Like Dermatitis Following Therapy With Mychrysin. Arch. Derm. & Syph. 62: 105-112 1940.

<sup>114</sup>Landau-Wall P. and Bonner J. Les éruptions hémorragiques post-auroiques. Sang. 8: 825-829 1933.

<sup>115</sup>Goussard, H. and Blass, P. Syndrome hémorragique déclenché tardivement par l'or. Bull. Soc. franç. de dermat. et syph. 40: 877-878 1933.

<sup>116</sup>Martensfeldt, H. Die Behandlung des Lupus erythematosus mit Kryodermia. Klin. Wchnschr. 1: 2325-2327 1933.

<sup>117</sup>Reichardt A. J. G. Onychia and Alopecia After Gold Dermatitis. Nederl. J. dermat. Geneskr. pp. 2612-2614 1937. Ed. 88: 308.

<sup>118</sup>Alkhan, M. L. Lichen Planus Due to Gold Therapy. Bull. Soc. franç. de dermat. et syph. 46: 24-42 1939.



large flat papules which have a tendency to coalesce into large plaques of the lichen cornuus type.<sup>1021</sup>

There are two kinds of skin *discoloration* known to follow the administration of gold. One is caused by deposits of *melanin* in the upper cutis. This type corresponds to the more common arsenical melanosis and is reversible. It frequently develops after gold rashes<sup>1022</sup> but it may also be primary and occur after small doses.<sup>1023</sup>

The second type is of greater and more practical interest. The injected salt is reduced to *metallic gold* and deposited in the lower cutis in the subcutis in the kidneys and in all parts of the reticulo-endothelial system.

The visible discoloration is restricted to the skin exposed to light. No difference in the gold content between discolored and apparently normal skin can be found by means of spectroscopic or histologic analysis.<sup>1024</sup> With the slit lamp gold particles can be demonstrated in the cornea.

The darkening is diffuse and slate to graphite gray in color. Most observers emphasize a bluish or purplish hue.<sup>1025</sup> The dyschromia seems to be permanent. Lorenzen<sup>1026</sup> found that none of his tuberculous patients who had received more than a total of 0.15 Gm. of sodium aurothiosulfate per kg body weight escaped chrysiasis but none of those with a total of less than 0.05 Gm per kg developed it. The trouble becomes visible one to three years after the treatment. Mild cases of *chrysiasis* as this discoloration caused by gold deposits is called do not as a rule constitute a very conspicuous disfigurement.

With the commonly used doses of up to 50 mg per injection the danger of producing chrysiasis is remote.

*Hyperkeratoses* and diffuse keratoderma after gold treatment are very rare.<sup>1027,1028</sup>

*Oral symptoms* of gold eruptions have frequently been described. Dryness and metallic taste are often the first symptoms of gold intolerance. Simple erythematous or vesicular stomatitis may occur with edema and ulceration of the tongue in severe cases. Gold stomatitis has been seen to precede rashes.<sup>1029</sup> Clinically and histologically typical oral lichen planus almost always without accompanying cutaneous lichen planus has been noticed relatively often<sup>1030, 1031, 1032</sup> as a sequel of gold intolerance. The lesions are white irregular thin or slightly

<sup>1021</sup>Gonggerot, Vial and Nakam. Lichen ou psoriasis verruqueux latense et très étendu. Bull. Soc franc de dermat et syph 63 1863-1885 1926.

<sup>1022</sup>Mary A Horowitz A and Souillard, J. Pigmentation en nappes et acné cornée consécutives à une érythrodermie aigue. Bull Soc franc de dermat et syph. 60: 1816-1819 1923.

<sup>1023</sup>Ingang A. Keratoderma and Melanoderma Accompanying Therapy With Gold Compound. Arch. Derm. & Syph 34 631-639 1936.

<sup>1024</sup>Kochs A G. Chrysiade. Arch f Dermat. Syph 578 323-330, 1938.

<sup>1025</sup>Schmid O E L. Chrysiade. Arch Dermat & Syph 48 446-452 1911.

<sup>1026</sup>Lorenzen, J. V. Ueber das Auftreten von Chrysiade bei früher mit Natriumaurothiosulfat behandelten Lungentuberkulösen. Beitr. Klin d Tuberk 28 696-800, 1971.

<sup>1027</sup>Reitberg, A C Page, A F M and Gordon H. Gold Dermatitis With Hyperkeratosis. Brit J Dermat 48: 127-142 1936.

<sup>1028</sup>Fearley L and Boltanski E. Gold Dermatitis. Rev d stomatol 28 891-898 1930; Ibid 23 679.

<sup>1029</sup>Fladerod C W. Lipo erythematodes der Mundschleimhaut. Arch f Dermat. Syph 163 218-222 1925.

<sup>1030</sup>Jochims, P H U. Lichen planus der Mundschleimhaut nach Goldbehandlung. Dermat. Wchnsch 99 1373-1378 1974.

popular keratosis of the buccal and labial mucosae.<sup>162</sup> They may disappear after discontinuation of the gold treatment.

A peculiarity of gold is its activating effect on chronic inflammations and infections, especially tuberculous foci. The appearance of papulonecrotic tuberculosis under gold treatment has been reported (Medina after Throne et al.<sup>163</sup>)

### Silver

While there is little known about acute toxidermia caused by silver this metal is more likely to cause permanent deposits and discolorations than any other metal. The *dyschromia* from silver is called *argyria*, *argyria* or *argyria*.

Occupational argyria has been seen in the chemical industry and among workers who blow a silver nitrate solution into glass beads or Christmas tree decorations to silver the inner surface. After many years in this trade such craftsmen sometimes become deep black with a metallic sheen.<sup>162,164</sup> Of much greater importance, though rarely reaching the same degree of discoloration is the argyria caused by the use of silver compounds in medical therapy.

Silver nitrate pills for peptic ulcer, tabes or epilepsy have gone out of fashion but the prolonged use of silver nitrate, mild silver protein or colloidal silver in nose drops<sup>165</sup> or in sprays or paints, and in genitourinary douches or instillations have produced a great number of cases of generalized argyria. Some cases were observed after injections of silver arsphenamines, now obsolete.<sup>166</sup> Gaul and Staud<sup>167</sup> state that after the injection of a total of 8 Gm. of silver arsphenamine argyria becomes clinically apparent.

The first darkening of the skin may appear as early as six months or as late as fifteen years after the initial use of the silver drug, but two to three years have been found as the average in 68 cases of the Mayo Clinic.<sup>168</sup>

It is remarkable that women outnumbered the males 7:4 in this series.

Argyria appears as a slate to bluish gray, sometimes bronzed,<sup>169</sup> rarely black, diffuse discoloration predominantly of the skin exposed to light.<sup>168</sup> Thus the forehead, face, neck, and the dorsa of the hands are the main sites of the trouble, but in severe cases the entire body surface may be involved. The conjunctivae may be stippled and the caruncles of the inner canthi, the gums and the palate have often been found slate colored.

<sup>162</sup>Lerist-Jacob and Legrain, P. *Lapses erythematosa rubra par* (or) *Apparition d'un Eclat* *plan buccal intense*. Bull. Soc. franç. d. dermat. et syph. 38: 766-767 1921.

<sup>163</sup>Throne, D., Kingsbury, J. and Myers, C. N. Unusual Clinical Manifestation Following Intravenous Administration of Gold Compounds. Arch. Dermat. and Syph. 38: 494-507 1932.

<sup>164</sup>Teletzky, L. Generalized Argyria. Ed. f. Dermat. 3: 124-133, 1: 12.

<sup>165</sup>Marker, J. M. and Hunter, D. Argyria. Brit. J. Dermat. 47: 441 1925.

<sup>166</sup>Wood and H. R. Argyria From the Use of Colloidal Silver Iodide Intracutaneously. Am. J. Dis. Child 48: 1948-1949 1933.

<sup>167</sup>Agelst, L. A Discoloration of the Skin and Mucous Membranes Resembling Argyria Following the Use of Bismuth and Silver Arsphenamine. Arch. Dermat. & Syph. 23: 260-268 1932.

<sup>168</sup>Gaul, L. E. and Staud, A. H. Clinical Spectroscopy. Seventy Cases of Generalized Argyria. J. A. M. A. 104: 1347 1940, 835.

<sup>169</sup>Hill, W. R. and Montgomery, H. Argyria With Special Reference to Cutaneous History. Arch. Dermat. & Syph. 44: 553-569 1941.

<sup>170</sup>Detahaver, Argyria. Arch. Dermat. & Syph. 23: 708, 1930.

<sup>171</sup>Stinson, A. W. Argyria. Arch. Dermat. & Syph. 38: 67-77 1927.

large flat papules which have a tendency to coalesce into large plaques of the lichen cornuus type.<sup>1001</sup>

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<sup>1001</sup> Gougeon, V. and Vekem. Lichen ou prurigo verruqueux intrane et très étend. Bull. Soc. franç. de dermat. et syph. 43: 1582-1583, 1936.

<sup>1002</sup> Meary, A., Horowitz, A. and Boiffard, J. Pigmentation en nappes et acné cornée consécutives à une érythrodermie aurogène. Bull. Soc. franç. de dermat. et syph. 40: 1018-1019, 1933.

<sup>1003</sup> Irigoin, R. Keratoderma and Melanoderma Accompanying Therapy With Gold Compound. Arch. Dermat. & Syph. 34: 624-629, 1936.

<sup>1004</sup> Koche, A. H. Chrysiasis. Arch. f. Dermat. & Syph. 178: 333-339, 1919.

<sup>1005</sup> Schmidt, O. E. L. Chrysiasis. Arch. Dermat. & Syph. 46: 448-452, 1911.

<sup>1006</sup> Lorenzen, J. N. Ueber das Auftreten von Chrysiade bei früher mit Kaliumaurothiosulfat behandelten Lungen tuberk. Klin. d. Tuberk. 78: 686-696, 1921.

<sup>1007</sup> Resburgh, A. C. Page, A. B. M. and Gordon, D. Gold Dermatitis With Hyperkeratosis. Brit. J. Dermat. 48: 137-142, 1936.

<sup>1008</sup> Fournier, L. and Boffanski, E. Gold Dermatitis. Rev. de stom. ol. 28: 681-686, 1936. Ebd. 23: 679.

<sup>1009</sup> Finckel, C. W. Lapsus erythematodes der Mundschleimhaut. Arch. f. Dermat. & Syph. 118: 218-222, 1925.

<sup>1010</sup> Fohrmann, B. H. U. Lichen planus der Mundschleimhaut nach Goldbehandlung. Dermat. Wechnchr. 99: 1373-1376, 1931.

of argyria but fails to do so in other metallic discolorations e.g. that caused by bismuth. This method of treatment has not yet found general acceptance mainly because it is quite painful<sup>61</sup>. Argyria is an almost permanent trouble. Only occasionally has spontaneous, usually incomplete, regression been reported.

### Lead

The skin in lead poisoning is said to be sallow and dry often itchy. Erythemas, pustular eruptions and petechiae occur<sup>62</sup>. The workers who have symptoms of lead poisoning show an incidence of dermatoses mostly dermatitis, which is about three times larger than among the workers in the same industry without symptoms of saturnism. The incidence is particularly high in the group with gastrointestinal disturbances. *Hemolporphyriaemia* which is common in chronic lead poisoning is a factor in the pathogenesis of these dermatoses.<sup>164</sup> <sup>63</sup> However actual sensitization of the skin to lead is very rare.<sup>64</sup> In rare instances metallic pigmentations have been seen. The well known *gum line* is a deposit of black lead sulfide produced by the hydrogen sulfide which develops in the tartar. The line is blue, black or gray and follows the edge of the gums. The removable deposits on the border of the gums may also be discolored.

Dystrophy and even loss of the nails from lead is known. Pain in the nails may indicate nervous disturbances.<sup>65</sup>

### Bi smuth

Bismuth may although very rarely cause diffuse blue-black discoloration of the entire skin which resembles argyria.<sup>66</sup> Circumscribed and in some instances extensive black pigmentations of the lips<sup>66</sup> vagina<sup>66</sup> and other mucosal surfaces have been described.

These however are rare considering the large number of luetic who have been treated with bismuth without any evidence of such discolorations.

<sup>164</sup>Fevert, A. Gewerbliche Schädigungen durch Hg, Pb, und Bi in Oppenheim, R.Ds., Ullmanns Fachschriften d. Haut durch Beruf und gewerbliche Arbeit, Vol. II Leipzig, 1928. Leopold Voss, pp. 161-167.

<sup>61</sup>Prkillyand, I. O. Role of Lead in Certain Dermatoses, *Soviet Arch. der.* 43: 547-568, 1939.

<sup>62</sup>Gegenheimer, E. *Deriatsen, Feb. der med. Wchnsch.* 63: 277-280, 1933.

<sup>63</sup>Kuorhord, W. and Mierkamp, W. *Häufigkeit, Derm. Wchnsch.* 193: 244-250, 1936.

<sup>64</sup>Schwartz, L. and Talipan, L. *Occupational Diseases of the Skin*, Philadelphia 1936, Lea & Febiger.

<sup>65</sup>Leach, H., Sutton, D. C. M. Miller, C. J. and Muchlberger, H. W. Generalized Discoloration of Skin Resembling Argyria Following Prolonged Oral Use of Bismuth. Case of Bismuthia, *Arch. Int. Med.* 57: 1118, 1936.

<sup>66</sup>Simons, E. H. Bismuthismus Nederl. Tijdschr. Geneesk. pp. 712-713 1937. *Id.* 86: 404.

<sup>67</sup>Wiener, K. Vaginal Melanosis Caused by Bismuth Therapy and Carcinoma of the Cervix *Arch. Dermat. & Syph.* 62: 23-29 1940.

*Pruritus nitritoid crisis*<sup>1803</sup> *urticaria morbilliform scarlatiniform pitiriasis rosea-like*<sup>1803 1802</sup> or *lupus erythematosus* resembling<sup>1804</sup> eruptions *acne*<sup>1805</sup> and *exfoliative dermatitis*<sup>1806-1808</sup> have occurred. They are rarer generally less severe and they do not have the importance of the corresponding arsenical phenomena<sup>1806</sup>



FIG. 181.—Blue line at gingival margin from bismuth medication

The only common surface sign of bismuth poisoning is the *blue gum line* which corresponds entirely to the blue line of lead. The bismuth line can often be observed during antiluetic treatment especially around lead teeth. The line disappears several months after the discontinuation of the treatment. Severe

<sup>1803</sup>Bertin, E. and Breton, A. Crises nitritoides consécutives aux injections de bismuth, Paris méd 2: 476-477 1932

<sup>1804</sup>deWalt, H. P. Dermatitis Medicamentosa Bismuth, Arch Dermat & Syph. 28 362-364, 1927

<sup>1805</sup>Fox, H. Carrara's Pigmentation and Dermatitis Following Bismuth Therapy Arch Dermat. & Syph 28 365-366 1937

<sup>1806</sup>Teyssie, G. and Teyssie, A. Accident cutané, non-déclaré encore, cours de traitement bismuthique efficace. Lésions erythroquameuses à sa cordon centrifuge simulant le lupus erythemateux. Napp. Congr Dermatologistes Langue franç 1935, pp 242-244

<sup>1807</sup>Thal, E. 4 al as rare accident della terapia bismuthica. Arco da bismuto, Boll. soc. rec. Ital. Dermat. 3 25 253, 1935

<sup>1808</sup>Woeber, G. & J. Macouchet J. and Bondey I. offensa bismuth. or hyperthermia, dermat. generalisée d'origine iv. albuminurie et polyneurite. Bull. Soc. franç. de dermat. et syph. 41 660-572 1977

<sup>1809</sup>Raumann, H. von & Dreyer, H. Xbl 68 376, 1931

<sup>1810</sup>Vicolas J. Roquet J. and Thomaux A. Erythrodermie importante cours d'un traitement par l'hydroxyde de bismuth. Bull. Soc. franç. de dermat. et syph 41 8 7-815, 1977

Reidert J. Erythrodermia bismuthica: les une syphilitique une fait erythrodermie arthritique (réd. dermat. pp 360-362 1931) Xbl 68 446

<sup>1811</sup>Jablenberg F. Die Nebenwirkungen der Wismuthbehandlung. Handb. d. H. u. Gk 18: 442-495, 1925.

ulcerative<sup>1001</sup> even fatal<sup>1002</sup> stomatitis or glossitis may also develop but this is much rarer than in mercury poisoning

## Mercury

It has almost been forgotten that mercury is able to produce the same types of rashes which occur due to arsenic, gold bismuth and other metals. Urticaria follicular and diffuse erythema morbilliform scarlatiniform and papular rashes and also exfoliative<sup>1003</sup> dermatitis are known. However they are less common and also less dangerous than the corresponding arsenical dermatoses. Macular rashes resembling erythema infectiosum were established as mercury eruptions due to the administration of calomel and the filling of dental cavities with amalgam<sup>1004</sup>. The rashes are often the only symptom of mercury intoxication<sup>1005</sup>. Scaling and diffuse or reticular hyperpigmentation may follow the erythroderma<sup>1006</sup>.

The most important surface symptom of mercurial poisoning is stomatitis Almkvist,<sup>1007</sup> who has devoted so much effort to the study of mercury poisoning suggested that  $H_2S$  which develops in the decomposition of proteins under the gums and in inaccessible pockets of the oral mucosa, forms  $HgS$  with the mercury carried by the bloodstream. He also found that mercury sulfide is more irritant to the oral mucosa than other metal sulfides. The first deposits of  $HgS$  are found in the loops of the capillaries of the papillae.

The first clinical symptoms are usually salivation metallic taste and a feeling of excessively long or dull teeth. Soon the gums start to swell and form pockets between themselves and the teeth in which pus is retained permitting prolonged contact of  $H_2S$  with the circulating mercury.

The inner lining of these pockets is the first site of superficial necrosis. From there the stomatitis which is soon complicated by infection spreads to the open surfaces of the gums where pseudo-membranes and ulcers quickly form if the process is not halted by treatment and discontinuation of the mercury. In severe cases, the entire mouth may become affected the tongue edematous the tonsils ulcerated the teeth loose and even pneumonia and fatal sepsis have in the days of the mercurial therapy of syphilis occasionally occurred<sup>1008</sup>.

Treatment consists of cleaning and disinfecting the pockets with thin pointed cotton applicators dipped in strong silver nitrate tincture of iodine or any other strong astringent and disinfectant. Naturally the teeth should be kept meticulously clean and another drug should be substituted for the mercury preferably the nonmetal penicillin.

<sup>1001</sup>Al trau Stomatitis ulcerosa et necroticans blennorrhagica, Zbl 96 441

<sup>1002</sup>Beerman H. Fatalities Due Plasmuth in the Treatment of Syphilis, Arch Dermat & Syph, 28: 797-801, 1932

<sup>1003</sup>Almkvist, J. Quecksilbervergiftungen, Handb d H. Gk 18 178-222, 1932.

<sup>1004</sup>Jacoby E. Ueber Quecksilbervergiftungen bei Kindern, Schwab med. Wchnskr 66: 942-943, 1920

<sup>1005</sup>Gaugerel, P. Blum, J. Brulez and Archambaud, R. Plagmation r6ticul6e oulqer pr6s erythroderme hydrangyrique Arch dermat-syph H6p St Louis 4 365-37 1932

<sup>1006</sup>Picard M., Mamez, G. and Tremereau Stomatite mercurielle gangreneuse mortelle, Bull. Soc. franc. de dermat et syph. 63 1803-1805, 1926.



Mees's bands in arsenic poisoning have been described<sup>87, 88</sup> and thallium has been found in the nails.<sup>89</sup> The local application of salve containing thallium acetate for the purpose of epilation has proved effective but has resulted in a great number of systemic poisonings.

### Carbon Monoxide

Carbon monoxide poisoning rarely causes skin manifestations. Shillito Drinker and Shaughnessy<sup>90</sup> did not mention any skin damages in their survey of 21 143 cases, but it seems that this report did not pay enough attention to the cutaneous symptoms.



Fig. 134 — Localized gangrene following carbon monoxide poisoning. (From Sheft, E. A. *J. M. Soc. New Jersey*.)

The cherry red lips and deep cyanosis of persons poisoned with monoxide gas is generally well known. Local edema of the extremities was known to the older observers. It may be related to the circumscribed necroses found after severe gas poisonings.<sup>91-93</sup> The lesions start as serous or hemorrhagic bullae which

<sup>88</sup>Adler A. Nagetveränderung bei Thalliumvergiftung. *Dermat. Wochschr.* 62: 226-261, 1922.

<sup>89</sup>Widder W. Fall von akuter Thalliumvergiftung. *Zbl. Bz.* 193, 1924.

<sup>90</sup>Shillito P. U. Drinker C. and Shaughnessy T. J. The Problem of Nervous and Mental Sequelae in Carbon Monoxide Poisoning. *J. A. M. A.* 196: 666, 1926.

<sup>91</sup>Bernstein R. Naschekrose bei Kohlenoxydvergiftung. *Zbl. Bz.* 626, 1922.

<sup>92</sup>Oppenheimer G. Umekriebene Hautgangrän und Purpura nach Leuchtgasvergiftung. *Zbl. Bz.* 191, 1922.

<sup>93</sup>Sheft, E. A. Factors in Peripheral Skin Lesions Following Carbon Monoxide Poisoning. *J. M. Soc. New Jersey* 49: 418-420, 1912.



develop into deep sharply outlined round ulcers or patches of dry gangrene. Such necroses have been seen on the heels, soles, ankles, cuffs, sacral area, fingers and scalp. In several cases an entire limb was affected.<sup>100,1000</sup>

Perhaps decubitus is at least in some cases a factor in the pathogenesis of the ulcers but there are clinical and histological reasons to blame primary vascular damage instead.

*Herpes zoster* especially of the forehead is considered to be a characteristic sequel of monoxide poisoning.<sup>1002</sup> (See also discussion to Fischel<sup>1001</sup>)

### Sedatives

The *barbiturates* quite frequently produce rashes of allergic character. Pruritus and urticarial macular scarlatiniform multiform or petechial exanthems are fairly common and well known especially from phenobarbital. Bullous eruptions in the mouth have also been observed.<sup>1003</sup> The severe and in some instances fatal cases of exfoliative dermatitis are fortunately very rare.<sup>1000</sup>

*Nirvanol* is a hypnotic which almost constantly produces a morbilliform exanthem after 8 to 14 days of regular administration. The rash is accompanied by conjunctivitis, stomatitis and other mucosal reactions, fever, cyanosis, diarrhea and other nervous symptoms, gastrointestinal and hepatic symptoms and albuminuria, a syndrome which is known as *nirvanol disease* (v. Pfaunder after R. L. Mayer<sup>1004</sup>). Nirvanol is used in the treatment of chorea. The therapeutic result depends on the development of the nirvanol allergy.<sup>1005</sup>

### Bromine

Morbilliform urticarial bullous vesicular vacciniform and other rashes are occasionally seen after the administration of bromides. More characteristic are acniform eruptions which appear at the predilection sites of acne vulgaris especially on and around the nose. It seems that bromine acne is more apt to suppurate and to form flaccid pustules than the common juvenile form.<sup>1006</sup>

In some cases *ulcers* form which by central healing and partial peripheral advance may resemble tertiary syphilis. A peculiar feature of some bromine reactions is the tendency to develop *tuberous* or tumor like vegetations. These bromodermas are known in several varieties and combinations. They occur as papillomatous confluent crustous suppurative or ulcerating sessile or tuberous usually painful eruptions. Small subepidermal abscesses in the edges of the lesions may create a blastomycosis-like picture. After the expression of pus from large lesions a quite characteristic cribriform surface results.<sup>1007</sup>

<sup>1000</sup>Easer, V. and Spilberg, S. Gangrene of Lower Extremity Following Carbon Monoxide Asphyxia. *Am. J. Clin. Path.* 18: 111-116 1910.

<sup>1001</sup>Fischel, C. K. Carbon Monoxide Asphyxia. New York, 1919 Oxford University Press.

<sup>1002</sup>Knaap, A. Seltene Fälle von Herpes Zoster. *München und Wchnacher* 87: 545-546 1910.

<sup>1003</sup>Fischel, S. Fälle von Hauterkrankungen bei Leuchtgasvergiftungen. *Wid.* 1: 107 1921.

<sup>1004</sup>Hofma, M. Phenobarbital Eruption of the Mouth. *Arch. Dermat. & Syph.* 25: 902, 1932.

<sup>1005</sup>Jacobsohn, K. Icher Barbiturate-Allergie. *Med. Klin.* 28: 199-201 1923.

<sup>1006</sup>Madison, J. F. Nirvanol Eruptions. *Arch. Dermat. & Syph.* 28: 1065-1073 1932.

<sup>1007</sup>Kirschberg, L. Toxicodermien. *Handb. d. H. u. Gk.* 8: 2: 253-276 1937.

<sup>1008</sup>Wetherston, E. W. Nodular Papillomatous Bromoderma. *Cleveland Clin. Quart.* 13: 19-29.

The bromodermas are most often seen on the lower legs and vary widely in size and number of lesions. There may be a few or several hundred and some may be as small as pins while others may reach the size of a fist.<sup>1992</sup> The various types of lesions may be seen in the same patient at the same time. A characteristic foul odor may be present.<sup>1993</sup>

The lesions have occasionally been first observed several months after the ingestion of bromine had been discontinued. Bromoderma sometimes develops out of other pre-existing skin lesions e.g. ulcers scars and injuries. The tongue and other parts of the mouth may participate in the fungating process.

The allergic character of the bromodermas has been recognized by most authorities but is disputed by some investigators<sup>1994</sup> mainly because of negative skin tests.



Fig. 158 — Acneliform eruption from bromine.

The passive transfer of the allergy to the guinea pig has occasionally been demonstrated.<sup>1995</sup> Bloch and Tenchio<sup>1996</sup> elicited in their case of severe bromoderma with fatal outcome positive patch tests after 24 hours. Later these reactions turned into bromoderma an interesting demonstration of Koebner's phenomenon.<sup>1997</sup> Positive scratch and intradermal tests have also been elicited.<sup>1998</sup> Excessive eosinophilia is another argument in favor of the allergic nature of the bromodermas. The vegetations have several times been found to be free of bromine. The diagnosis of the bromine dermatoses has to consider such heterogeneous diseases as the acute exanthema, acne vulgaris, syphilis, blastomycosis, epithelioma, mycosis fungoides, erythema nodosum and others.

<sup>1992</sup>Leibner, K. Bromoderma, *Id.* 83: 228, 1936.

<sup>1993</sup>Acosta, E. I. Bromoderma Vegetans, *Veren. J. Dermat.* 8: 83-86, 1921.

<sup>1994</sup>Bloch, B. and Tenchio, P. Bromoderma Vegetans, *Arch. f. Dermat. Syph.* 185: 83-148, 1925.

<sup>1995</sup>Flammarion, K. Bromoderma und Histallergie, *Arch. f. Kinderh.* 129: 103-107, 1937.

<sup>1996</sup>Norahardt, R. Acne bromata provocata, *Arch. f. Dermat. u. Syph.* 171: 113-114, 1924.



Fig. 157.—*Bromoderma tuberosum* (From Neiberton, E. W. Cleveland Clin. Quart.)



Fig. 158.—*Bromoderma tuberosum* (From Neiberton, F. W. Cleveland Clin. Quart.)

The copper or brownish hue of the bromodermas is often emphasized.

Discontinuation of the bromides and large amounts of fluid and sodium chloride<sup>170</sup> are important in the treatment.

The prognosis of treated cases is generally favorable if the use of bromides is discontinued. Scarring and pigmentation are common sequelae. Rarely the lesions continue to develop despite discontinuation of the drug and treatment. Such cases may end fatally.<sup>170</sup>

### Iodine

The eruptions following the internal use of iodine and its compounds follow the pattern of those produced by bromine. Acne is the most common dermatome of iodism. Vesicular bullous,<sup>100</sup> and hemorrhagic eruptions have been seen more often than the vegetating forms. The allergic nature of the iododermas and the sensitizing effect of iodized table salt<sup>107</sup> has been established by experimental investigations.<sup>102</sup>

Fatal cases of Iododerma tuberosum are very rare.<sup>105-110</sup>

### Some Other Drug Eruptions

Almost all drugs and poisons are able to produce allergic skin eruptions. Among the great number of multiform morbilliform, scarlatiniform, eczematoid, hemorrhagic, bullous, vesicular and other exanthems a few stand out because of unusual clinical features.

*Phenolphthalein* eruptions are well-defined round or oblong red and later purplish brown spots. They sometimes appear as large bullae. The macular lesions are lentil to palm sized and are most often seen about the buttocks and the lower back, but also on the extremities.

The bullae are large and deciduous leaving an erythematous and pigmented base. Eczematous forms are less well known. The lesions may after an inflammatory stage recede and leave only a faint pigmentation. It is a peculiarity of the phenolphthalein eruptions to appear in exactly the same sites, even after complete or almost complete disappearance and after long intervals. This is known as a fixed eruption.

<sup>100</sup>Wigle, I. J. Further Contributions to the Experimental Aspects of Iodid and Bromid Exanthema. Arch. Dermat. & Syph. 8: 407-410, 1933.

<sup>101</sup>Spillmann, W., and Malton. Dermis bullense généralisée d'origine iodique chez une hémiparétique (JBU Soc. franç. de dermat. et syph. 98: 1264-1268, 1933).

<sup>102</sup>Becker, P. E. Iodized Table Salt as an Etiologic Factor in Iododerma. Arch. Dermat. & Syph. 23: 829-836, 1971.

<sup>103</sup>Kischel, H. Eine seltene Form - Iododerma hem. Jap. J. Dermat. 32: 130-131, 1932. Ed. 43.

<sup>104</sup>Holander, L. and Fetterman, G. H. Fatal Iododerma. Arch. Dermat. & Syph. 31: 224-241, 1936.

<sup>105</sup>Herszenberg, H. and Moschikofson, L. Ueber Thrombangiitis obliterans (Beitrag z. Pathogenese des Iododerma bullorum veritatis) Beitr. path. An. allg. Path. 94: 243-260, 1934.

<sup>106</sup>Kelley, J. J. and Fox, E. C. Fatal Iododerma. Arch. Dermat. & Syph. 29: 745-757, 1921.

Phenolphthalein is an ingredient of more than a hundred proprietary laxatives.<sup>1182</sup> Similar fixed eruptions also occur as a reaction to *antipyrin*.<sup>1183</sup> The eruption to either drug may develop within an hour after ingestion. Severe melanoderma after phenolphthalein is very rare.<sup>1184</sup>

*Sedormid* a mild sedative of the urea group has in many cases caused severe thrombocytopenic purpura.<sup>1185 1187</sup>

*Veramon* a popular European combination of barbital and amidopyrin may give rise to fixed symmetrical eczematous patches and mucosal swellings. Its use has been discouraged because of the danger of *agranulocytosis* from the amidopyrin content.

*Quinine* eruptions are most often scarlatiniform. In severe cases exfoliative dermatitis may develop. Severe purpura is a rare event. About one out of 200 patients is or becomes allergic to quinine.<sup>1188</sup>

*Atabrine* which proved to be a satisfactory substitute for quinine may cause a lemon to sickly greenish yellow discoloration<sup>1189</sup> after one to four months of use. The yellow dychromia is uneven. In contrast to icterus with the heaviest discoloration on the exposed parts and in the folds of the body. The sclerae remain white. The extensor<sup>1190</sup> surfaces of the arms and feet the webs, the nape the forehead and the circumoral area are most deeply stained. A golden ring around the mouth is a peculiarity of the atabrine pigmentation. Unlike the discoloration in carotinemia the palms are less yellow than the dorsa of the hands.

Bluish pigmentations have been seen in the hard palate epiglottis tracheal rings, and the nail beds.

During the war in the South Pacific, especially in New Guinea many cases of a dermatosis with features both of an *atypical lichen planus* and *eczematoid dermatitis* occurred among the troops who took atabrine regularly for the suppression of malaria but it is not generally recognized that atabrine is the cause.<sup>1191</sup> The condition is characterized by various combinations<sup>1192</sup> of purplish hypertrophic lichenoid papules and plaques frequently with a rough verrucous surface and eczematoid plaques in all stages of erythema oozing and scaling

<sup>1182</sup>Belet G H and Whitney H A K Phenolphthalein Compounds, Arch. Dermat. & Syph. 94: 278-281 1937

<sup>1183</sup>Ilasek G and Balason J Plaques érythémato-pigmentées fix et éphémères basées à type érythème polymorphe par ingestion d cachets à base d antipyrine, Bull. Soc. franç. d. dermat. et syph. 42: 453-455, 1933.

<sup>1184</sup>Waher, R S Dermatitis Medicamentosa (Phenolphthalein) Arch. Dermat. & Syph 23: 1182, 1931.

<sup>1185</sup>Falcover E N and Schumacher J C Purpura Hemorrhagica Due to Ingestion of Sedormid (Alyl-isopropyl-acetyl-carbamide) Arch. Int. Med 88: 122-127 1940

<sup>1186</sup>Lowy F E Thrombopenic Hemorrhagic Purpura Due to Sedormid. Allergotonic Effect, Lancet 1934 I 643-644

<sup>1187</sup>Huber H Case of Purpura Hemorrhagica Resulting From Sedormid, J A M A. 113: 874-875 1936

<sup>1188</sup>Haas A Leber Chlaminintoxikation und Chlaminidiosynkrasie Deutsche med. Wchnschr 61: 223-224 1935

<sup>1189</sup>Schechter A J and Taylor H M A abrine Pigmentation A J M Sc. 192: 645-650 1936.

<sup>1190</sup>Epstein, E Lichen Planus-Eczema-oid Dermatitis Complex of South est Pacific Bull U S Army M Dept 8: 657-663, 1943

<sup>1191</sup>Loward Reactions Attributed to Atabrine (A typical Lichen Planus) J A M A. 129: 1091 1093 1918

The dermatosis may also though rarely consist of lichenoid elements alone. More frequently the eczematoid lesions dominate the picture entirely even to the extent of severe generalized *exfoliative dermatitis*.

The legs and forearms, the dorsal surfaces of the hands and feet and the face neck buttocks and genitalia are predominantly and symmetrically affected. Atrophy and hyperpigmentation, nail changes, and shedding of the nails patchy alopecia and dyshidrosis have been described as late sequelae.

With the exception of severe exfoliative dermatitis, the course is generally benign if atabrine is discontinued.

*Picric acid* may cause generalized *yellow discolorations* which simulate icterus. The sclerae take part in the staining.

The *sulfonamides* may cause a great variety of eruptions which are essentially the same as those due to the barbiturates the arsenphenamines and many other drugs. A special feature is the frequent *photo-sensitization* caused by the use of sulfonamides.

*Ephedrine* besides occasionally causing generalized erythemas and dermatitis has, in some persons, a tendency to produce urticaria and local swellings, especially of the eyelids.<sup>12-14</sup>

*Codeine* rashes<sup>15</sup> have been described as follicular erythemas which quickly develop into scarlatina like exanthemas. Codeine and opium occasionally produce pruritus or formication.<sup>16</sup> Paresthesias are also a dominant symptom in chronic *ergotism* from<sup>17</sup> *Claviceps purpurea* infected rye and wheat and in *ustilaginism* from corn infected with *Ustilago maydis*.<sup>18</sup> Even *acrodynia* like cases of *morbus cerealis* have become known. In *farism* a severe poisoning occasionally caused by the eating of broad beans (*vicia faba*) purpura is an important symptom.<sup>19</sup>

*Dinitrophenol* the dangerous weight reduction agent caused urticarial macular maculo-papular and eczematoid rashes in 7 to 20 per cent of the treated persons.<sup>20-22</sup> The frequent *yellow discoloration* is due to the staining and is not caused by icterus.<sup>23-25</sup>

<sup>12</sup>Trudeau, S. S. Francis, K. and Parker J. M. Dermatitis Medicamentosa, Due to Ephedrine J. Allergy 3 443-444, 1933

<sup>13</sup>Ayres, S. J. and Anderson, M. P. Dermatitis Medicamentosa Due to Ephedrine, J.A.M.A. 97 437-440, 443-445 1933

<sup>14</sup>Abrahamson, E. W. and Koss, M. H. Ephedrine Dermatoses, Brit. J. Dermat. 45 225-227 1933

<sup>15</sup>Scheer, M. and Keil, H. The Skin Eruptions of Codeine, J. A. M. A. 192: 909-910 1924

<sup>16</sup>Ossendrick, W. V. Alleviation and Treatment of Itching, Practitioner 142: 23-24 1920

<sup>17</sup>Kawata, J. Chronic Endemic Ergotism Its Relation to the Vasomotor and Trophic Disorders, Arch. J. Med. 47: 541-564 1921

<sup>18</sup>Mayrhauser, E. Ustilaginism, eine bisher unbekannte Form akuter Störung bei der Maiskultur im Kleidersterbend. Festschr. 8 183-187 1931. Zbl. 29 778.

<sup>19</sup>Jimenez-Diaz, C. and Viel, O. M. Anaphylactoid Purpura Due to Sensitization Beans (Purpura Form of Fabius) Rev. clin. españ. 5 129-130, 1942.

<sup>20</sup>Freeman, O. M. Allergic Reaction to Dinitrophenol (Case J. A. M. A. 192: 1219-1920 1934

<sup>21</sup>Lucas, B. M. Dermatitis Medicamentosa Formula 261 (Dinitrophenol) Arch. Dermat. 4 579-581 273-275 1933

<sup>22</sup>Finckh, J. Dinitrophenol and Desiccated Thyroid in Treatment of Obesity J. A. M. A. 100 2110-2117 2182-2 99 1937

## CHAPTER XIV

### DISORDERS OF THE CIRCULATION

#### *Heart Disease*

Cardiac decompensation no matter what its cause may be produces a rather uniform syndrome with dyspnea cough palpitation and precordial distress dominating the complaints. Cyanosis and edema are almost always present

**Cardiac Decompensation**—*Cyanosis* is not only caused by the deficient blood circulation. If the state of decompensation lasts for some time the respiratory system suffers and the oxygenation of the venous blood becomes insufficient increasing the cyanosis. Cyanosis is an early sign of valvular heart disease especially of the right heart but also though later of the mitral valves. It is less pronounced in aortic insufficiency.<sup>122</sup>

Extreme degrees of cyanosis are encountered in the *newborn* infant with congenital affections of the heart. In contrast to the cyanosis in acquired and adult types of heart disease the blue discoloration may cover the entire body surface of the baby (*Morbus caeruleus*). In later life the cyanosis is usually restricted to or at least most marked in the acra. The cheeks the lips the nose the ear lobes the finger tips, the toes the elbows and the patellae are chiefly affected.<sup>123</sup> Frequently only a slightly purplish hue of a seemingly healthy complexion indicates an underlying cardiac insufficiency. The cyanotic parts especially the feet and lower legs are cool.

If cyanosis exists for a longer period sharply drawn *telangiectases* appear. On the face they resemble *rosacea* or they are the first stage of *rosacea*. *Telangiectases* occur also on other parts of chronically congested skin e.g. between the shoulder blades and on the abdomen.<sup>124</sup>

*Edema* usually is seen first in the skin about the ankles but later it may involve the entire skin and the subcutaneous tissues. Chronic congestion may cause *clubbing* of the fingers and toes more so in children than in adults.<sup>125</sup>

The skin in chronic congestion is if not yet cyanotic, *pale* and often grayish. Slight *hemorrhagic* tendencies are an early sign of decompensation though they may be only detected by the tourniquet test or the capillaroscope.<sup>126</sup> Naegeli mentions extravasations over the thorax and epigastrium in decompensated mitral insufficiency.

The *pallor* of the patients with mitral stenosis before the cyanosis occurs is marked.

*Hyperpigmentation* occurs—especially in children—on the forearms and the dorsa of the hands and fingers. The pigment is *hemosiderin* from the extravasa-

<sup>122</sup>Beckel H. *Chronische tau nephren beim Kinde*. Monatsschr f Kinderk 48: 294-303 1927.  
<sup>123</sup>Jürgensen K. *Ökult Hautblutungen*, Deutsches Arch. f Klin Med 178: 84-854 1927.

tion<sup>122, 428</sup> Slight *jaundice* is frequent. It appears less pronounced in the edematous parts.<sup>428</sup> Increased *freckles* are often seen in juveniles with decompensated mitral insufficiency.<sup>122</sup>



FIG. 189.—*Dermatitis* of legs, exacerbating and receding, with cardiac decompensation.



FIG. 190.—*Dermatitis* of legs, hypertensive. Parallelism of exacerbations with degree of cardiac decompensation.

<sup>122</sup>Kaufmann E. Die pathologischen Veränderungen der Haut. Handb. d. H. u. Gk. 4: 2 1911 1221 1922.



*Hypertrichosis* is a symptom of chronic congestion in children. The back, the face, and the extensor aspects of the extremities exhibit the increased lanugo most distinctly.<sup>1127</sup>

*Eczema* of the lower legs, sometimes with a purpuric component is an occasional accompaniment of decompensation. The healing with improvement of the circulation and relapse on recurrence of decompensation is proof of the circulatory factor in these eczemas.



Fig. 161.—Schamberg's dermoids in circulatory stasis. (Courtesy Dr. M. Jesner.)

The *pulsating erythema* of the nail bed or of a dermatographic line known as the capillary pulse is a well known sign encountered in aortic insufficiency but also in other conditions. The jerking pulsation can be demonstrated in the capillarscope.<sup>1128</sup>

### Arteriosclerosis, Hypertension

Arteriosclerosis affects the arteries of the skin<sup>1127</sup> as well as those of other organs (see Chapter on Old Age). The capillaries appear tortuous and thin in the capillarscope (E. Weiss after B. Niekau<sup>1129</sup>).

The clinical skin changes produced by arteriosclerosis are best observed in the feet.<sup>1130</sup> The skin is dry due to the impairment of the glandular functions. The nails become atrophic and brittle or thick. Corns and calluses become thicker. The lanugo hair on the dorsa of the phalanges disappears. The foot including the sole may become cyanotic on dependence and pale on elevation.

<sup>1127</sup> Nikan, B. Kapillarbroscheln an der Körperoberfläche des Menschen, *Ergeb. d. inn. Med. u. Kinderh.* 22: 479-551, 1922.

<sup>1128</sup> Weismann, A. Beiträge zur Pathologie der Gefässerkrankungen der Haut III. Mitt. Die Arteriosklerose der Haut. *Dermat. Wchnschr.* 102: 69-75, 1926.

<sup>1129</sup> Niekau, B. Cutaneous Manifestations of the Circulatory Disorders of the Feet. *J. A. M. A.* 124: 747-750, 1914.

Nomland<sup>128</sup> believes that the more nearly horizontal the leg is when pink color returns the greater is the insufficiency of the arterial supply. Wounds and infections even trivial ones heal slowly and may cause severe complications. This is the more important since *pruritus* is a common symptom of cutaneous arteriosclerosis and decompensation.<sup>129</sup>

*Cardiac infarction* may leave its mark in cross furrows of the nails (Beau's lines) or more rarely in transversal white lines.<sup>130</sup> Cross furrows have also been observed on the toenails in intermittent claudication.<sup>131</sup> Occasionally an *erythema* of the face and neck resembling *erythema pudoris* has been seen in *angina pectoris*<sup>132</sup> and *hypertension*.<sup>133</sup>

*Herpes Zoster intercostalis* has often been related to *angina pectoris*.<sup>134, 135</sup>

The most important though by no means constant cutaneous manifestation of hypertension is *pruritus*. It is often severe and reflects in its intensity the ups and downs of the blood pressure. Severe attacks of *pruritus* may precede apoplectic episodes. Rarer than *pruritus* alone are *eczematous* or *pruriginous* changes. It is in such cases hard to decide whether the dermatosis is due to hypertension, nephrosis or decompensation since it may accompany all of these conditions. The *eczema* sometimes seems secondary to *prurigo*, the itching papulo-tourticarial lesions of which are quickly destroyed by scratching. A slight scab-covered spot of lentil to fingernail size ensues. Groups of such lesions in various stages of development and lichenification are usually found along the legs and in some severe cases over the entire body. These cases are at least temporarily benefited by superficial X-ray therapy.

In obstinate cases of *eczema* of the hands, of nummular *eczema* and of scaling and itching of the finger tips one should consider the state of the circulation and treat accordingly.

Hypertension, aortitis, arrhythmia, chronic glomerulo-nephritis and other vascular and hepato-splenic disorders may be accompanied by pigmented and depigmented hemorrhagic inflammatory plaques on the lower legs. Favre<sup>136</sup> and his collaborators have stressed the internal relationship of this condition which he called *angiodermatitis pigmentosa purpurica*. He stressed that this common syndrome has nothing to do with varicose veins and that it does not show the features of *eczema*. The underlying periosteum is often early affected. The patches run a gamut of colors from yellow to blue-black. The surroundings are often depigmented. The lesions are also variable in size and contour. Hemorrhagic infiltration with formation of a black scab and ulceration occurs.

<sup>128</sup>Coburn, G. *Pruritus als dyspathisches Symptom mit Bemerkungen über pruriginöse Dermatitis*, Arch. f. Derm. 82:1, back, 2. 1945.

<sup>129</sup>Wahl. Cross furrows of the Finger Nails Following Cardiac Infarction, Arch. Dermat. 83: 108-107 1945.

<sup>130</sup>Archelslager, H. Das Nagelsymptom bei dem intermittierenden Hinken, Med. Klin. 28 831-833, 1930.

<sup>131</sup>Paronah, A. and Flora, G. T. Angine de poitrine d'effort, no erythème initial et possible hypertension, Bull. et mem. d. Soc. med. Hôp. d. Paris 67: 1630-1652, 1921.

<sup>132</sup>Weber, F. F. Dermatic Blotchy Flushing Over Neck and Upper Thorax in an Elderly Woman With High Blood-Pressure, Proc. Roy. Soc. Med. 28: 731 1935.

<sup>133</sup>Arveria, J. Herpes zoster bei harten Organverwachsungen, Deutsche. med. Wochenschr. 62 908-909, 1920.

Tenderness and scaling are other features. The pigment is hemosiderin. In spite of some similarities the common angiodermatitis is to be separated from Shamberg's disease and from purpura Majocchi. Syphilis is the most common etiologic factor.

The compression of the superior vena cava by an *aneurysm* of the ascending aorta may cause congestion and tortuosity of the veins of the neck and face even of almost the entire upper half of the body. There is also edema and cyanosis. Pressure on one of the innominate veins produces these signs on one side only usually the left.<sup>12</sup> A leaking aneurysm of the abdominal aorta may cause huge saggulations of the scrotum and lumbar area.



Fig 102. Female aged 17 years. Arteriovenous aneurysm following fracture of radius. Increased growth of the affected hand, large parosteohemangioma, coiled vessels, increased skin temperature, hyperhidrosis and bruits. (Patient of Dr. Karl Achlaschky.)

Peripheral arterio-venous aneurysms are usually caused by trauma. They cause hemangioma like accumulations of tortuous blood vessels with pulsation and murmurs. The skin over such a lesion is warmer than normal and perspires more readily. The increased blood supply causes increased growth of the involved part including the bones.

### Thrombo-Angiitis Obliterans (Buerger's Disease)

In this disorder of unknown but <sup>126</sup> probably bacterial etiology <sup>127</sup> the peripheral arteries and vein of the leg—rarely of the arms—sometimes together with adjacent nerves <sup>128</sup> are affected. Arteries with thrombus formation in single or

<sup>126</sup>Buerger, L. The Circulatory Disturbances of the Extremities. Philadelphia and London, 1922.  
W. B. Saunders Co.

<sup>127</sup>Allen, E. V. Thromboangiitis Obliterans. Bull. New York Acad. Med. 18: 103-149, 1917.

Klauer, R. Thrombo-Angiitis Obliterans. Buerger. Acta orthop. Scandinavica. 31: 103-122, 1971.  
Ela 29: 550, 1931, 1932.

multiple foci causes a state of ischemia with severe pain. The pain may occur on exertion and then it has the character of intermittent claudication or it may be experienced while the patient is at rest. In this case the pain is continuous, worse at night and sometimes aggravated<sup>1137</sup> and sometimes eased by dependency. Gangrene with severe pain may occur. The course of the disease is most often chronic and slowly progressive in attacks. The peripheral pulses in the affected limb are absent or diminished. The sufferers are almost exclusively young men (98 per cent) often Hebrews (28 per cent) and heavy cigarette smokers (93 per cent).<sup>1138</sup> Familial incidence has been observed.<sup>1139</sup>

**Dermadromes**—The skin of the toes is at least in the fairly advanced stages, moist, cool often scaly tender and reddish-blue in patches especially if the patient stands. Elevation blanches the limb. Reactive hyperemia is apt to follow on lowering the leg except in severe cases.<sup>1139</sup> If the time required for the return of color while in the dependent position is longer than 10 seconds impaired arterial circulation exists. In marked impairment of the arterial circulation by thrombo-angitis the return often takes more than forty-five seconds.<sup>1137</sup> Refilling of veins after emptying by elevation also takes longer than ten seconds. Superficial palpable phlebitis is a feature in Buerger's disease which leaves hemosiderin pigmentation for a long time after healing.

Variable degrees of pallor or cyanosis may follow exposure to cold or emotion.<sup>1137</sup> If gangrene develops it is less extensive than in arteriosclerosis because of the smaller caliber of the thrombosed arteries. It is usually of the moist type. The endangered toes are bluish especially the nailbeds. The skin is often glossy and atrophic. Subungual keratosis develops frequently. Ulceration of the big toe is the commonest form of necrosis. Gangrene of the fingers is much rarer than gangrene of the toes since the establishment of collateral circulation has a better chance in the arms than in the legs. Besides the occlusion by thrombosis vasospasm plays a part. The diagnosis has to exclude arteriosclerosis. Here the picture is very similar but the patients are older the pain at rest is milder gangrene is more apt to be dry and phlebitis and edema are not features. Lipema is frequent in arteriosclerosis and the arteriosclerotic artery may be detected by X-ray.<sup>1140</sup>

The treatment requires complete abandoning of smoking, vascular exercise by systematic raising and lowering of the legs, and warm baths. Mechanical pulsating devices do not seem to be very effective in Buerger's disease. Amputation, nerve section or sympathectomy are often necessary.<sup>1137, 1141</sup>

## Shock

Shock is characterized by circulatory failure and deep depression of the nervous functions. It may be caused by trauma, hemorrhage, massive infection, burns, intestinal perforation, cardiac failure and other conditions.

<sup>1137</sup>Horton, B. F. Thrombo-angitis obliterans, 919 Cases. Incidence of Amputation, *Ann. Surgeon* 54: 509-520, 1929.

<sup>1138</sup>Wickstrom, K. Arteritis obliterans (Thromboangitis Buergeri) als familiäre Erkrankung. *Deutsche Arch. f. klin. Med.* 171: 291-296, 1931.

<sup>1139</sup>Hecman, B. Circulatory Diseases of the Extremities, New York, 1939. The Macmillan Company.

In shock the effective circulating blood volume i.e. cardiac output and venous return is reduced and the peripheral flow of blood is slowed down<sup>11</sup>. The blood pressure is at first maintained by vasocompensatory mechanisms but drops as soon as these mechanisms become weak. While in the initial or premonitory stage of shock the pulse may not be altered it becomes rapid and thin in the fully developed syndrome.

**Dermadromes.**—Di Palma<sup>12</sup> stresses the diagnostic importance of the skin phenomena in the initial phase the knowledge of which may enable the physician to apply help before the onset of deep shock. For the examination the patient has to be stripped and remain exposed to room temperature for at least 10 minutes. If the skin can be blanched by pressing the forefinger forcibly into it some blood must be in the skin. The color contrast with the unblanched skin and the rate of fill-in of the blanched areas permit quick though rough and unreliable estimate of the peripheral blood flow. Gentle touching with the back of the digits permits the determination of gross differences between the skin temperature of the trunk and the extremities. Such differences would indicate a slow blood circulation in the periphery. The color of the skin is an excellent guide in the estimation of the rate of the peripheral blood flow. It should be judged by the hue of the cheeks the lips and especially of the nail beds. Di Palma<sup>12</sup> advises the acquisition of competence by observing the nail beds under controlled conditions of circulation produced by a blood pressure cuff and varying elevation of the arm. Brick red purplish and finally deep purplish blue indicate the degrees of peripheral circulatory failure.

Since the brick red hue is an early sign it is most important. Simultaneous forcible stroking of the skin with a blunt instrument on the chest and on the forearms provides an opportunity to compare the differences between the time of appearance and the color of the red dermographism. The peripheral blood flow must be considered slow if the red line appears later than five seconds and if the reaction on the forearm is delayed in comparison with the chest. The color should be bright red. DiPalma, Moss and Foster<sup>13</sup> have devised a method which measures the minimal time required to elicit hyperemia by a weighted rubber ring placed on the skin of the chest and arm (stimulus time) and the time after which the hyperemia fades (clearance time). These times are compared with those obtained from a normal person in the same room.

<sup>11</sup>DiPalma, J. R. The Circulation in the Skin I. the Shock Syndrome. *J. A. M. A.* 123: 641-663, 1943.

<sup>12</sup>DiPalma, J. R., Moss, J. and Foster, F. I. Reactive Hyperemia Ring Test in the Study of Prolonged Lesions Caused by Arteriosclerosis Obliterans and Arterial Embolism. *Am. Heart J.* 21: 312-361, 1912.

## CHAPTER XV

### DISEASES OF THE KIDNEYS

The relation of dermatoses to renal disorders fascinated the physicians of the nineteenth century more than the recent generations. Bright, in 1827 was convinced of the sympathy between the skin and the kidney and many famous authors have investigated this relationship more closely.<sup>20</sup>

The kidneys being concerned with the excretion of water-soluble substances are functionally linked to the skin. Under normal conditions the skin stores about 28 per cent of the body's water. It takes up much more in edema<sup>114</sup> which is the dominant symptom in acute diffuse glomerulonephritis and in some stages of other renal diseases. The loose texture of the skin and of the subcutaneous tissue affords more storage space than the muscles or even the serous cavities are able to provide. Along with water the skin stores chlorine and minerals. The vast vascular capacity of the skin provides an important regulating mechanism of the blood pressure which is the main power behind the urinary excretion. The skin has an excretory function which however can only partially and occasionally replace renal excretion.<sup>115</sup>

Under normal conditions the skin as well as the kidneys excrete about 1300 c.c. of water daily but the kidneys are able to concentrate from the blood more than thirty times more urea and three times more NaCl than the tubules of the sweat glands. Thus even a damaged kidney usually excretes better than the skin and the skin alone is not able to replace the function of the kidneys.

Dermadromes were seen in approximately one-fifth of the series of 1100 patients with all forms of nephritis and nephrosis studied by Chargin and Keil.<sup>116</sup> These authors found that skin diseases occur more frequently in association with azotemia than in those without azotemia. In contrast to earlier observers<sup>117</sup> they found that purpura is the most frequent lesion associated with nephritis. All types of hemorrhagic lesions ranging from pinpoint petechiae to large extravasations were encountered. Chronic glomerular nephritis without edema seemed to predispose to hemorrhage far more than the other clinical types of nonsurgical kidney disease. Higher degrees of azotemia often cause intense purpura. Sometimes the hemorrhagic tendency expresses itself only in a hemorrhagic component of a usually nonhemorrhagic dermatoses e.g. urticaria. Pruritus varying widely in intensity and in its sequelae may be the first symptom of nephritis (Oenlatory after Pringle<sup>118</sup>). It occurred in 20 per cent of the cases of essential hypertension with azotemia and in 12 per cent of the instances of

<sup>114</sup> Krone C. Die klinischen Zusammenhänge zwischen Haut- und Nierenerkrankungen, Zbl. 61: 30 1922.

<sup>115</sup> Zimmer K. Schrifttümliche Verhandl. d. Gesellsch. f. Verdauungs- Stoffwechsel II 213-221, 1927.

<sup>116</sup> Pringle J. J. Skin Eruptions in Bright's Disease Practitioner 127 840 1901.

chronic glomerular nephritis with edema. Its infrequency in all other groups of the series of Chargin and Keil<sup>229</sup> is striking. Azotemia is probably the inciting factor. Azotemia without pruritus occurs, but if pruritus is present in uremia it is regarded as of serious prognostic importance.<sup>230</sup> The pruritus may be explained by *dermatitic changes* which Rösle observed in almost all of 25 cases of



FIG. 163. Purpura. Chronic nephritis.

uremia even when no gross changes were present.<sup>231</sup> These inflammatory changes ranged from simple perivascular infiltration to necrotic and herpetiform pandermatitis. The findings could not be confirmed entirely in an American series. Here atrophy of the skin was the dominant pathologic feature. Other pathologists have cautioned not to overrate the perivascular infiltration in the skin,<sup>232</sup> which is often seen in glomerulonephritis.

The urea content of the skin is usually high. The appearance of crystalline urea as a thin white saltlike deposit on the skin, especially about the nose, the

<sup>229</sup>Rösle R. U. *Kutische Dermatitide*. Virchow Arch f path Anat 271: 304-316 1920.

<sup>230</sup>Rosenbal H. H. *Uremic Dermatitis*. Arch Derm & Syph 22: 971 1921.

<sup>231</sup>Hershelmer C. and Roemer W. *Hautveränderungen bei Nephritis*, Munchen med. W. kocher

neck and the shoulders<sup>131</sup> is known as *urea* (uremic) *frost*. It occurs most frequently in malignant sclerodermis and essential hypertension (10 to 20 per cent after Chargin and Keil.<sup>132</sup>) A prolonged agonist period which allows the formation of the crystals together with a high urea content of the blood and of the skin seem to be the factors accounting for its relative frequency in these conditions.<sup>133</sup> The phenomenon of urea frost is more often seen post mortem than in life. It is still controversial whether the source of the urea frost is the sweat glands or the sebaceous glands. Its accumulation in the areas of accumulated sebaceous glands and its absence on the palms and soles seems to support the sebaceous gland theory while observations of crystals at the mouth of the sweat glands seem to prove the sweat gland origin. Urea frost is of ominous prognostic significance.

*Erythematous bullous and urticarial eruptions* in nephritis<sup>134</sup> have occasionally been described. Generalized exfoliative dermatitis is also mentioned in connection with the renal disease.<sup>135</sup> Some of these dermatoses may have been caused by septicemia. Ehrmann<sup>136</sup> saw in edematous patients aggregated vesicles about the head which rapidly formed oozing pink surfaces.

*Flasural eczema* is supposed to be more common in nephritis without edema. Grouped papular eruptions of great obstinacy were in the older literature known as *erythema papulatum uremicum*<sup>137</sup> (Merk after Ehrmann<sup>138</sup>)

It may be mentioned in this connection that rabbits with experimental glomerular nephritis could be shown to be more sensitive to skin irritation from tar than the normal controls.<sup>139</sup>

A progressive febrile dermatosis probably of bacterial origin occurring relatively often in *lipid nephrosis* is referred to as *erysipeloid*. (This condition should not be confused with the erysipeloid of Rosenbach.) The eruption is seen on the abdomen and thighs spreading from there with an erythematous circinate finish and tender border. There may be recurrent attacks<sup>140</sup> with occasional abscess formation.<sup>141</sup>

The complexion of patients suffering from *contracted kidney* is often yellowish. This discoloration is restricted to parts exposed to light. The pigmentation is explained<sup>142</sup> by the retention of urochromogens which under the influence of light change into their color just as they do in a pale urine from an arteriosclerotic kidney. There is no retention of urochromogens in acute nephritis.

<sup>131</sup>Jachs, O. Erythema exudativum multiforme und Erythematosen innerer Organe, Arch. f. Dermat. Syph. 23: 33-72, 1909.

<sup>132</sup>Darkeuth, H. A Case of Chronic Interstitial Nephritis in Which Dermatitis Exfoliativa Supervened, Ark. J. Derm. 12: 1900.

<sup>133</sup>Ehrmann, A. Beobachtungen der akuten Nieren Erythematosen zu Landen Leiden. Halle 1924, Carl Mielckel.

<sup>134</sup>Krischanek, A. La réactivité de la peau et la fonction des reins, Ann. de dermat. et syph. 7: 652-70, 1926.

<sup>135</sup>Melick, C. A. and Boyle, H. H. Erysipelas-Like Lesions of Skin in Nephrosis, Am. J. Dis. Child. 84: 559-183.

<sup>136</sup>Schwarz, H. and Kohn, J. L. Bacteremia and Skin Manifestations in Lipid Nephrosis, Am. J. Dis. Child. 38: 703-774, 1929.

<sup>137</sup>Becher, E. Untersuchungen über das Zustandekommen der gelblichen Hautfärbung bei Niereninsuffizienz. München med. Wochenschr. 77: 1922, 1930.



Carotinemia is always present in nephroses but only in 10 per cent does the skin become noticeably yellow<sup>1187</sup>

In acute nephritis the capillarscope may reveal narrow arterial and wide tortuous venous segments. The subpapillary venous plexus is well visible and the circulation is slowed. These changes may precede the outbreak of nephritis<sup>1188</sup> (Goth after Niekau<sup>1189</sup>) suggesting the primarity of the capillary damage.

*Herpes zoster* has often been seen in attacks of nephrolithiasis<sup>1190</sup>. Severin<sup>1191</sup> found that these eruptions corresponded to the eleventh and twelfth dorsal and the first and second lumbar segments. Their area was found identical with the associated Head's zones. Some cases of pruritus and obstinate eczema in chronic nephrolithiasis were relieved by operation. They can be interpreted as caused by the infected focus and by parenchymal damage caused by calculi and infection.

Pruritus is a common symptom in all types of chronic urinary retention. Thus it is frequently and early observed in benign hypertrophy of the prostate and occurs also in stricture of the urethra. It is good advice to examine prostate and bladder in all unexplained cases of pruritus and secondary pyoderma present in elderly men.<sup>1192,1193</sup> In rare instances pruritus vulvae may be caused by nephropoiesis.<sup>1194</sup>

Though not being the cause of dermatoses *Peyronie's disease* or induration of the tunica albuginea of the corpora cavernosa penis is possibly a manifestation of a systemic disorder which may also cause surface symptoms. Touraine and Ruel<sup>1195</sup> call hereditary polyfibromatosis the tendency to form nodular nonencapsulated indurations in many parts of the connective tissue. While the association of induration of the corpora cavernosa with Dupuytren's contraction of the palmar aponeuroses has long been recognized keloids, fibromas of the fingers and similar connective tissue lesions are also seen together with Peyronie's disease. Simple dominant heredity is supposed to exist. Similar hypotheses of earlier authors have not found acceptance.<sup>1196</sup>

<sup>1187</sup>Boeck, W. G. and Lister, W. M. Xanthemia and Xanthosis (Carotinemia). *J. Lab. & Clin. Med.* 14: 1123-1143 1920.

<sup>1188</sup>Lutz, W. Stoffwechsel und H. wt. Handb. d. H. Ok. 3 1920.

<sup>1189</sup>Strickler, A. Plots of kidney as Cause of Pruritus Vulvae, *Arch. Dermat. & Syph.* 30: 405 1914.

<sup>1190</sup>Touraine, A. and Ruel, R. Hereditary Polyfibromatosis, *Ann. de Dermat. et Syph.* 8: 1-5, 1910.

<sup>1191</sup>Kedersid, W. Dupuytren'sche Kontraktur und Nierf. *Arch. f. Gesamtepath. Gewebelehre* 2: 33-47 1923.

## CHAPTER XVI

# DISORDERS OF THE ENDOCRINE GLANDS

## THE PITUITARY BODY

The hormones of the *anterior lobe* of the pituitary stimulate the activity of the thyroid the parathyroids the mammary glands the islands of Langerhans in the pancreas the adrenal cortex the gonads and the placenta. The carbohydrate and fat metabolism and the growth are influenced either directly or indirectly by the effects on the above-named glands.<sup>109,110</sup>

The *intermediate lobe* activates the melanophores in the skin of amphibia. Its physiology in man is little understood.

The *posterior lobe* secretes two principles which act on the smooth muscle fibers. It profoundly influences diuresis by the production of an antidiuretic hormone.

### Fröhlich's Syndrome

*Dystrophia adiposogenitalis* or *Fröhlich's Syndrome* is the triad of obesity particularly of the lower trunk genital underdevelopment and pituitary symptoms. The latter seem due to hypoadactivity of the anterior lobe and the pars intermedia. Fröhlich's Syndrome is one of the commonest endocrine diseases especially of young males. This was demonstrated in the induction centers during the last war.<sup>111</sup>

**Dermadromes.**—In the younger patients the skin is smooth and pale and the veins are well visualized. Cushing remarks that persistent freckles on exposed areas is a characteristic of most cases of hypopituitarism. Perspiration is scant or lacking.<sup>112</sup> The subcutaneous fat which is particularly abundant on the hips sometimes seems to suggest a deep seated nonpitting edema. Striae are seldom seen. The pubic and axillary hair is absent and the lateral third of the eye brow is often missing. Ordinarily the scalp hair is not only unaffected but seems to be especially well developed. If the under-developed gonads start functioning e.g. after successful treatment with anterior pituitary hormone the body hair and the other secondary sex characteristics may still develop. Several authors emphasize the small thin under-developed nails which do not show lunulae at their bases. Onychogryphosis fragility of the nails and opaqueness of the nail substance have occasionally been noticed.

<sup>109</sup>Barrington, E. L. Endocrine Therapy in General Practice Chicago Ill. 1940, Year Book Publishers Inc.

<sup>110</sup>Ryderman, E. H. Hormones of the Anterior Lobe of the Pituitary Body J A M A 123, 1911.

<sup>111</sup>Barstow. Endocrine Diseases as Revealed by 12,000,000 Examinations of Registrants, J Clin Endocrinol 4 5-24 1944.

<sup>112</sup>Cushing, H. The Pituitary Body and Its Disorders, Philadelphia, 1912.

In the rare *Laurence Moon Biedl* syndrome which consists of dystrophia adiposogenitalis retinitis pigmentosa mental deficiency and polydactylism cutaneous peculiarities other than in Frölich's syndrome have not been recorded

L. Fränkel noticed the failure of the lateral parts of the escutcheon to develop in patients with *pituitary infantilism* (After Musulo Fournier <sup>11</sup>)



FIG 164 Frölich type Male aged 18 years. Obesity gynecomastia, lack of pubic hair

The complete absence of secondary sex characteristics, dryness of the skin, freckles and hypotrichosis of body and scalp is the rule in *dwarfs of pituitary origin* (Type Loran Levi). The scalp loses some or much of its hair mostly in the vertex area less so at the margins. This vertex type of alopecia has been observed in several pituitary conditions (Engelbach). *Cutis laxa* and *Ehlers Danlos syndrome* has in some cases been related to hypopituitarism <sup>1</sup>

### Ca hexia Pituitaria Simmonds Disease

*Simmonds Disease* occurs almost exclusively in women after childbirth. The cause is atrophy or destruction of the glandular part of the pituitary.

The early stages of this syndrome resemble myxedema. Later with increasing wasting amenorrhea or in the male impotence develops. Muscular weakness, extreme loss of fat, hypotension, apathy and hypersomnia, low temperature, low blood sugar, low basal metabolism and eosinophilia compose a picture which can easily be confused with other cachectic conditions. Good and sometimes dramatic results have been obtained with anterior lobe extracts.

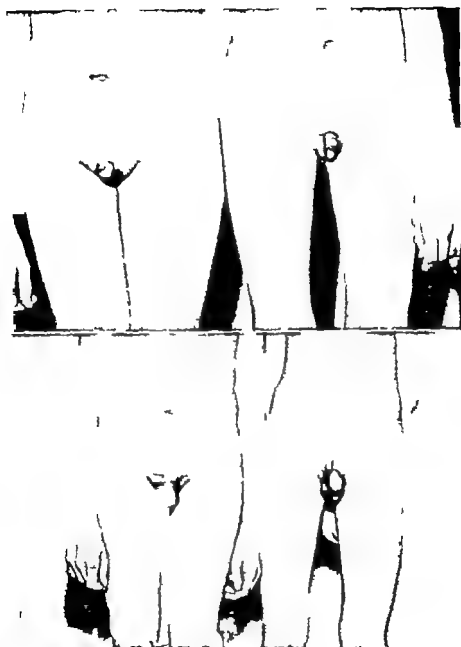


Fig. 63 — Brothers, aged 24 and 27 years. Arrested sexual development — he age of 14. Fröhlich type. Almost no pubic hair obesity. Below after one year of treatment. With gonadotropic hormone and testosterone. (Courtesy Wisconsin General Hospital)



Fig. 166—Laurence-Moon-Biedl syndrome. Not polydactylism (Courtesy Wisconsin General Hospital)

**Dermadromes.**—The skin is waxy, pale or yellowish and slightly edematous. Later the turgidity disappears and the skin becomes dry, wrinkled and slightly scaly or in some areas especially about the hands and feet glossy, chilblain like or even sclerodermatic. There is a definite tendency toward pigmentation. The pubic and axillary hair as well as the eyebrows and beard disappear completely in the fully developed syndrome<sup>100,101</sup>. In some instances not a single lanugo hair can be detected on the whole body surface. The eyelashes and the scalp hair usually stay. The nails and teeth fall out or suffer dystrophic changes.<sup>71</sup>

### Acromegaly

Acromegaly is caused by hyperactivity of the eosinophile cells of the anterior pituitary which are responsible for the growth stimulating hormone. Eosinophile (acidophile) tumors and eosinophile hyperplasia have often been found.

The overgrowth affects the skeleton and other systems. Maxillary rather than mandibular prognathism is characteristic of the true acromegalic. The nasolabial folds deepen and the ears seem to be set back. The teeth become separated and the hands and feet enlarged. The viscera take part in the unnatural growth. The hyperfunction of the anterior pituitary may be followed by hypo-

<sup>100</sup>Berthelauer W. Zur Klinik der akromegalen Krankheit. Endokrinologie 18: 259, 1931.

<sup>101</sup>Die akromegale Krankheit. (Anfrage Med. Kl.) 22: 59, 65, 912, 117, 1934.

<sup>102</sup>Zollackan J. Dermatologische Bezüge gegen die akromegale Krankheit. Dergory. 1934. 11: 177, 179, 183. 224, 241, 273.

<sup>103</sup>Cow. Hal F. on clinical alla connessa della sindrome di Simmonds (carcinoma ipofisaria). Policlinico sez. med. 28: 31, 264, 97.

<sup>104</sup>Herman H. Zur Klinik der akromegalen Krankheit. München med. Wchnsch. 77: 1020, 1930.

<sup>105</sup>Graubner W. Die hypophysäre Krankheit. akromegale Krankheit. Z. f. klin. Med. 191: 219, 1925.

function and incomplete regression of the acromegalic signs in the soft tissues.<sup>100</sup> Such a regression in the skeletal system is hardly possible. Therefore the typical cutaneous signs of acromegaly may be absent in fully developed skeletal acromegaly.



FIG. 167.—Acromegaly. Not freeless small fibrous deepening of furrows especially nasolabial and nasolabial folds. Ear seems to be set back. Courtesy Wisconsin General Hospital.

**Dermadromes.**—In acromegaly the skin like the bones and the viscera, is overdeveloped in every direction and can be compared to a normal skin under a magnifying glass. The surface is coarse the furrows deepened and the connective tissue thickened or somewhat edematous. Moles may appear or existing ones grow. Combination with Recklinghausen's disease has been observed a number of times.<sup>79</sup> The cutaneous glands are enlarged and their hyperactivity indicated by moisture and seborrhea. Comedones and follicular keratosis are marked. Acne is not uncommon. The pigmentation is moderately accentuated.<sup>101</sup> The hair growth is increased in about one-fourth of the cases, occurring<sup>102</sup> especially on the body so that in women a more masculine habitus results. In only seven per cent does the hair growth decrease.<sup>79</sup> By feeding young rats or injecting young dogs with anterior lobe extract the hair has been shown to become thicker than in the control.<sup>103</sup> (Robertson 1917 after Munro

<sup>100</sup> A. Lissac, F. R. B. Acromegaly. From Study of the Liver, no. 92 (1921). *Endocrinologie* 11: 265-280, 1926.

<sup>101</sup> A. Lissac, F. R. B. Acromegaly. London: 922 John Hale Street & Drabman, Ltd.

<sup>102</sup> R. A. W. and L. A. R. H. Studies of the Endocrine Glands. II. The Pituitary. *Endocrinology* 12: 2: 5-222, 1923.

<sup>103</sup> D. A. L. M. Acromegaly. *Endocrinology* 1: 401, 1928.

Robertson, E. Influence of Pituitary Feeding Upon Growth and Sexual Development. *Endocrinology* 11: 27-49, 1926.

Fournier<sup>114</sup>) Occasionally blond hair becomes darker and straight hair becomes curly and negroid<sup>117</sup> The scalp hair may become thin on the vertex<sup>117a</sup> and premature greying may be seen The nails participate in the general hypertrophy becoming broad striated sometimes spoon-shaped (colonychia)<sup>115</sup>

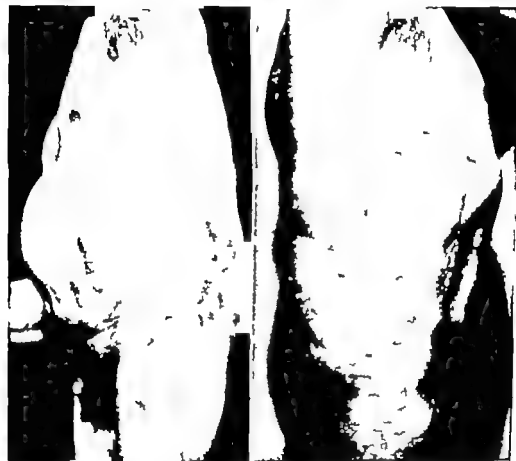


Fig. 169

Fig. 169a

Fig. 169 Cushing syndrome Broad purplish striae obesity (Courtesy Wisconsin General Hospital.)

Fig. 69 Broad purplish striae in Cushing's syndrome (Courtesy Wisconsin General Hospital.)

and occasionally long (Walker after Atkinson<sup>117</sup>) Varicose veins are not uncommon

*Cutis verticis gyrata*<sup>118</sup> is a congenital anomaly consisting of an excess of scalp which causes the skin of the vertex to form folds and furrows resembling

<sup>114</sup>Aascher H Der Einfluss der Hypophyse auf die weiblichen Geschlechtsorgane Med. Klin. 28 1 16-3 1924

<sup>115</sup>Kagelbach W Hair Growth and Pigmentation, M. Clin. North America, 9 1-41 1925

<sup>117</sup>Jadassohn J Eine eigenartige förmliche Erweiterung Verdickung d. Haut am Hl. u. Kopf. 9th Congr. Deutsch. dermat. Ges. Bern, 1906.





is often described as a full moon face but the facial expression is more painful than jolly. Weakness, kyphosis, back aches, amenorrhoea in the female and impotence in the male are other symptoms.

**Dermadromes.**—The most striking dermatome is the development of broad purplish striae atrophicae mainly in the lower and lateral parts of the abdominal skin. They were present in all of Cushing's twelve cases and have since been seen in a great number of instances.<sup>100</sup> It seems as if the basophile adenoma produces a toxic substance with a special affinity to the elastic fibers. Their resistance and elasticity appear to be weakened so that they tear on relatively slight strain (see striae of pregnancy).



FIG. 171.—Cushing syndrome. Livedo reticularis. (Courtesy Wycoast General Hospital.)

The skin is often hyperpigmented<sup>101</sup>. It is dusky or copper colored especially the face. It is usually dry. Purpura traumatica has frequently been observed.

Hypertrichosis of the face and trunk has been constantly found in females and preadolescent males.

Many secondary endocrine disturbances are on record such as those due to dysfunction of the thyroid and adrenals. Diabetes has been recorded.

The resistance against infections is lowered; this leads to frequent pyoderms. Infections are often the immediate cause of death.

<sup>100</sup> Jones: Cushing Syndrome. Med. Klin. 1936: 614.

## CHAPTER XVII

# DISORDERS OF THE ENDOCRINE GLANDS

### THE THYROID GLAND

Thyroxin the hormone of the thyroid gland stimulates the oxidative processes of the body

The influence of the thyroid on the skin is manifold.<sup>1187</sup> The removal of the gland in animals increases the content of water and chlorides the total nitrogen and the protein derivatives in the skin. Administration of thyroxin decreases the cutaneous chlorides and the water and increases the sugar and nitrogen. Some of these effects may be reversed with high doses of thyroxin. Thyroidectomy increases the capacity of the skin to swell in 1/10 normal HCl (Quellung). Thyroxin causes higher and more prolonged skin and blood sugar tolerance curves. The resorption time of a saline wheal is prolonged after thyroidectomy and shortened under the influence of thyroxin while the resorption of potassium iodide shows an opposite tendency. Thyroxin increases the sensitivity of the skin to X-ray and ultraviolet rays.<sup>1188</sup>

#### Hyperthyroidism (Grave Disease Basedow's Disease Thyrotoxicosis Exophthalmic Goiter)

The skin in hyperthyroidism is smooth thin and elastic with a velvety feel.<sup>1189</sup> This is in part a constitutional characteristic and is often present before any symptoms of the disease become apparent. The skin is moist warm and rosy but the color is unstable. The elevation of the temperature is roughly proportional to the increase in the metabolic rate. The difference in temperature between covered and exposed skin areas is less pronounced than in a person with a normal metabolism. It seems that the thinness of the skin as well as the increased temperature and moisture helps to free the body from a surplus of heat created by the elevated metabolism. The patients usually complain of excessive warmth and like to sleep with the limbs uncovered.

Dermadromes.—Erythema of the chest and back and of the parts where the clothing presses is common.<sup>1190</sup> Unexpectedly the capillary microscope shows that the capillaries are thinner than normal<sup>1191</sup> although observations of enlarged

<sup>1187</sup>Dohnstedt, R. M. Experimentelle Untersuchungen über die Beziehungen zwischen Haut und innersekretorischem System, Arch. f. exper. Path. 179: 474, 1931-1933.

<sup>1188</sup>Krämer, F. Über die Bedeutung der Schilddrüse für den Ablauf der Strahlungsreaktionen an der Haut, Klin. Wochenschr. 11: 1049, 1932.

<sup>1189</sup>Yocum, J. B. Changes in the skin in Thyrotoxicosis, Am. J. M. Sc. 231: 821-822, 1931.

<sup>1190</sup>Keen, E. P. The Thyroid, Springfield, Ill. 1933, Charles C. Thomas.

<sup>1191</sup>Michael, H. and Paschke, W. Über das Verhalten der Hautcapillaren beim Morbus Basedowii, Klin. Wochenschr. 11: 1863-1865, 1932.

capillaries have also been made.<sup>112</sup> Dilatation of the arterioles of the subcapillary plexus accounts for the increased rate of the peripheral blood flow and the high skin temperature (Bansl after Michael and Buschke<sup>113</sup>). Due to the increased moisture the electric resistance of the skin is low.

*Hyperhidrosis* is often as marked and as weakening as in pulmonary tuberculosis.<sup>114, 115</sup> Seborrhea, acne and comedos indicate overactivity of the sebaceous glands. In about 50 per cent of the cases<sup>116</sup> there exists a tendency to increased *pigmentation*. The hyperpigmentation is often inconspicuous this explains the much smaller percentages in some series. Youmans<sup>117</sup> sees a difference from the pigmentation in Addison's disease mainly in its lesser degree and in the lack of pigmentation of the mucous membranes. The pigmentation seems to have the older authors more impressed than those of recent years.<sup>118</sup> The hyperpigmentation of the eyelids is often regarded as suggestive of hyperthyroidism (Jellinek's sign).

*Vitiligo* has been seen in roughly 10 per cent of the cases.<sup>119, 120</sup> This is high enough to warrant a basal metabolism test in all cases of vitiligo.

There exists a marked tendency to transient *edema*. Unexplained puffiness of the eyelids<sup>121</sup> and ankles chronic *urticaria*<sup>122</sup> and angioneurotic edema should cause the physician to think of hyperthyroidism. The resorption-time of intradermally injected saline (McClure-Aldrich test) has been found to be prolonged in untreated cases with a return to normal after operation or iodine treatment.<sup>123</sup> The validity of these findings however has been disputed.<sup>124</sup>

*Marfan's sign* is the more marked and longer lasting red dermographism in the skin covering the thyroid gland as compared with the red dermographism in other areas. The sign is frequently positive in hyperthyroidism but is not specific.<sup>125</sup>

The *hair* is very sensitive to the toxic effects of hyperthyroidism. Sainton<sup>126</sup> and his collaborators noticed diffuse or circumscribed loss of the hair in 43 per cent of their 180 cases. The vertex and the temples are especially affected.<sup>127</sup>

<sup>112</sup>Roberts, E. and Griffith, J. B. J. Quantitative Study of Cutaneous Capillaries I. Hyperthyroidism, *Am. Heart J.* 15: 699-702 1937.

<sup>113</sup>Michael, M. and Buschke, W. Das Verhalten der Hautcapillaren beim Morbus Basedowii, *Dermatol. med. Wochenschr.* 59: 134-135 1933.

<sup>114</sup>Hyde and M. Kwon. The Dermatoses in Exophthalmic Goitre, *Am. J. Sc.* 125: 1000 1902.

<sup>115</sup>Stranell, H. Anemia and Diseases of the Blood-forming Organs and Ductless Glands, 1909.

<sup>116</sup>Habermehl, R. Paratyphische Pigmentanomalien, *Handb. d. H. Gk.* 4: 3: 795-824 1932.

<sup>117</sup>Dora. Cutaneous Affections Occurring in the Course of Graves Disease, *Brit. J. Dermat.* 12: 383 1900.

<sup>118</sup>Roosel, J. N. Chronic Urticaria, Thyro-Adrenal Syndrome, How to Determine the Direction of the Dysfunction, and What Type of Agents to Employ in Treatment, *Ann. N. Y. Acad. Sc.* 5: 645-672 1929.

<sup>119</sup>Mora, J. M. I. Iodine Solution Test in Thyrotoxicosis, *Am. J. Sc.* 127: 219 1929.

<sup>120</sup>Esroux-Ryan, R. Le signe de Marfan et sa signification dans le goitre exophtalmique. Thèse de Paris 1926.

<sup>121</sup>Sainton, P. and Rimmonet, H. Les troubles de la fonction thyroïdienne et leur action sur le système nerveux. A. de méd. 29: 262-270 1931.

<sup>122</sup>Sainton, P. and Marnet, H. Hyperthyroïdisme provoqué par la thyroxine synthétique chez un malade atteint d'un syndrome pluriglandulaire avec acrodermie et cataract. Bull. et mémoires Acad. méd. d. hôp. de Paris 43: 1645 1927.

<sup>123</sup>Forrester, O. H. The Relation of Internal Secretions to Cutaneous Disease, *J. Cutan. Dis.* 31: 1 1914.

Typical *alopecia areata* is not infrequently associated with hyperthyroidism an observation already made by Basedow.<sup>1241,1242</sup> Alopecia as well as canities may affect the head hair the beard the eye lashes the eyebrows and the body hair. Some authors emphasize the frequency of alopecia of the lateral third of the eyebrows. White spots in the hair have often been recorded.<sup>1243</sup> Improvement of the hyperthyroid condition may be followed by improvement of the alopecia. Universal baldness as well as hypertrichosis are rare.<sup>1247</sup>

Alopecia as well as canities has been experimentally produced in animals by feeding with human or animal thyroid or with thyroxine.<sup>1244,1245</sup>

Melanization however has also been observed after thyroid feeding.<sup>1246,1247</sup> Chickens are much better fit for these experiments than cats and rabbits.<sup>1248</sup> The sudden production of alopecia and canities after mental shock and terrifying experiences, which so far has not been well substantiated could be explained by sympathetic stimulation of the thyroid.<sup>1249,1250</sup>

In thyroidectomized rabbits regeneration of plucked hair is delayed or absent.<sup>1251,1252</sup> Thyroid extract feeding speeds the regeneration of plucked feathers in pigeons.<sup>1253</sup>

There is no relation between the severity of the hair changes and the severity of the hyperthyroidism. This refers to the clinical observations as well as to the animal experiments. The blood of thyroidectomized horses compensates the effect of thyroid feeding on the integuments.<sup>1254</sup> The extract of toxic goiter is reported to be more effective on the plumage of chickens than the extract of simple goiter.<sup>1255</sup>

In spite of these and other suggestive experiments the etiology of *alopecia areata* has not been elucidated. It seems that many factors are able to produce

<sup>1241</sup>Van Basedow O A. Kropfkrankheiten durch Hypertrophie des Schilddrüsens in der Augenschilddrüse. Wochenschr. f. d. ges. Heilk., Berlin, 1840.

<sup>1242</sup>Sabouraud R. Diagnostic et traitement des affections du cuir chevelu, Paris, 1922, Masson et Cie.

<sup>1243</sup>Payet, J. Dystrophies et dyssynchronies des formations épidermiques au cours du syndrome d Basedow (Météorisme exophtalmique). Thèse de Paris, 1926.

<sup>1244</sup>Scherevbrinsky N A. De l'influence des excréments endocriniens sur la peau des poils, Rev. franç. d'Endocrinol. 9: 201-212, 1922.

<sup>1245</sup>Zavadzki B. Effect of Single Doses of Thyroid Gland on Feeds, Endocrinology 11: 123-126, 1923-24.

<sup>1246</sup>Zavadzki, B. M. Hormone und das Gefieder der Vögel, Endokrinologie 10: 22-26, 1922.

<sup>1247</sup>Cole and Reid. Melanization After Thyroid Feeding, J. Agricul. Research 22: 1924.

<sup>1248</sup>Cove and Huxley. Melanization of Chicken Feathers After Thyroid Feeding, Vol. 2, W. 79, 1922.

<sup>1249</sup>Hatton, P. Maximal M. and Mamon, H. Hyperthyroidismus et son action sur les phanères, Bull. Soc. franç. de dermat. et syph. 25: 27, 1929.

<sup>1250</sup>Lévy Franchet, A. and Jaster E. Recherche sur le mécanisme physiopathologique de la pelade, II. Pérides traumatiques et pelades par choc émotif, Ann. de dermat. et syph. 24: 1074-1082, 1921.

<sup>1251</sup>Ramel. Posttraumatische Alopecia areata, Ekt. 44: 253, 1923.

<sup>1252</sup>Harber H. W. Post Traumatic Alopecia Areata, Amer. Roy. Soc. Med. 25: 922-923, 1922.

<sup>1253</sup>Farkas K. Beiträge zur Physiologie der Drüsen. Wachstum der Haare und Schilddrüse, Abhandl. Naturf. 157: 423, 1924.

<sup>1254</sup>Cosper Z. K. Endocrine Glands and Hair. Review of Literature Arch. Dermat. & Syph. 21: 1807 (1929).

<sup>1255</sup>Larsson W. Th. Weithewiller, A. A. and Frisky N. W. Die Regeneration des Gefieders der Tauben bei verschiedenen humoralen Einwirkungen, Endokrinologie 12: 8-22, 1923.

<sup>1256</sup>Sabouraud, R. H. Ramonnet, and Barbé P. Action comparée des extraits de glande thyroïde de bœuf et de goitreux sur le plumage des gallinacées, Bull. Soc. franç. de dermat. et syph. 27: 254-256, 1920.

the same typical picture which is more than twice as common in men as in women<sup>1226</sup> Infection<sup>1221, 1222</sup> seems plausible in a number of cases. Hyperthyroidism as well as hypothyroidism<sup>1223</sup> has been seen too often in alopecia areata to be dismissed as a coincidental occurrence<sup>1222-1226</sup>

Fig 172.

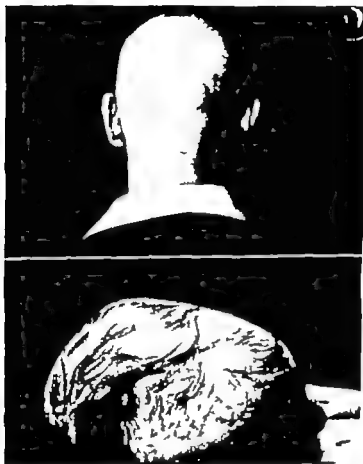


Fig 173

Fig 172 — Alopecia totalis. Moderate hypothyroidism.

Fig 173 — Same patient after treatment with thyroids

<sup>1226</sup>Wakeman, M and Kepler E J Alopecia Areata. An Appraisal of Endocrine Factors in Its Causation. J A M A 136 2004-2006 1941

<sup>1226</sup>Cederberg, A Über Versuche über die Alopecia areata mit besonderer Berücksichtigung ihrer Ätiologie. Speziell ein Beitrag zu V. Hingemann. Dermatol 47 235-242 1911 Ebl 49: 234

<sup>1226</sup>Wpfler, R Zu Ätiologie und Symptomatologie der Alopecia areata. Arch. f. Dermat. u. Syph. 122: 26 1939

<sup>1226</sup>Throne, J Nasal Metabolism f. Dermatological Conditions, New York Stat. J. Med 39: 254-263, 1930

<sup>1226</sup>Rubav, Y Zu Pathogenese der Alopecia areata. Czech dermatol 12 55-78, 86-102, 107 194, 125-141 1923 Ebl 45 435

<sup>1226</sup>Stojakovic Alopecia areata und Ocularis Ebl 39: 142 1921 1923

<sup>1226</sup>Sternlander Alopecia areata mit bedeutenden Thymusstörungen, Ebl 41 343 1922-1923

Weisman and Kepler<sup>1229</sup> found a metabolic rate of less than minus 10 per cent in 15 per cent of their cases.

The occasionally striking success of thyroid medication supports to some extent the thyroid etiology of some cases, though the general stimulating effect of thyroid preparations has to be taken into account. A pituitary etiology has been claimed on the grounds of (1) supposed roentgenological changes in the sella turcica<sup>1226-1227</sup> which was not confirmed by Wassman and Kepler<sup>1228</sup> (2) coincidence with pituitary symptoms and (3) successful treatment with anterior lobe extracts<sup>1226-1227</sup> and radiation of the pituitary.<sup>1229</sup> There are some cases with ovarian testicular and adrenal findings in alopecia areata with corresponding hormone therapeutic results. There are other arguments in favor of a pituitary etiology. Vitiligo or chloasma was present in about 10 per cent of Wassman and Kepler's<sup>1229</sup> series. The influence of mental strain and shock is important. Preceding infections have also been accused.

The nails have occasionally been found altered in hyperthyroidism. Longitudinal and transverse grooves, atrophy onycholysis and leukonychia have been described.

### Hypothyroidism

However different the symptomatology of congenital and acquired thyroid deficiency may appear there is little difference in the dermatomes of both types. The dermatomes of hypothyroidism appear early and therefore they deserve particular attention.<sup>1230-1231</sup> It is necessary to emphasize that the fully developed syndrome is rare while cases having some of the symptoms occur quite frequently. Severe deficiencies of the thyroid have been observed with or without skin changes.

In hypothyroidism the skin is pale and often slightly yellowish due to carotenemia.<sup>1232-1234</sup> It seems that the liver is unable to form Vitamin A from carotene due to the lowered metabolism. The skin is cool to the touch and the patient feels the cold more intensely than normal persons. The coolness of the skin is considered to be one of the earliest symptoms in the whole syndrome of hypothyroidism. The lowered temperature is especially noticeable in the ex-

<sup>1226</sup>Elder: Alopecia Totalis and Pseudis, Arch. Dermat. & Syph. 29: 603, 1923.

<sup>1227</sup>Takahashi: Ueber auffallenden Heberfolg des Hypophysen- oder Lappenhormons gegen Alopecia, Jap. J. Dermat. pp. 328-329 1933. Ed. 48: 193, 1933.

<sup>1228</sup>Wassman and Kepler: An error of Pituitary Therapy in Alopecia Totalis, Clin. Med. & Surg. 49: 891, 1931.

<sup>1229</sup>Takahashi, and Akahashi K: Weitere Erfahrungen aus der Hormontherapie der Alopecia areata, nach histologisch-chemischen, od. neurologischen Untersuchung, Jap. J. Derm. & Urol. 11: 1933.

<sup>1230</sup>White A W: Pituitary Extracts in Treatment of Alopecia, Canad. M. A. J. 21: 301, 1931.

<sup>1231</sup>Urbach E: Erfolgriche Röntgenische Therapie bei endokrin bedingtem Haarausfall, Ed. 23: 210, 1930.

<sup>1232</sup>Frederick A: Chronic Insufficiency of the Thyroid Gland, Real. Ven. Dermat. 5: Nos. 4-10, 1927. Ed. 23: 160.

<sup>1233</sup>Kras-Apajakakis L: Wirkung der Thyroideabehandlung auf die Haut des Myxödemkinder, Histochemische Untersuchungen, Acta Soc. med. Deodrina. 18: 2: 113, 192. Ed. 49: 630, 1932.

<sup>1234</sup>Karamella R F: Carotinemia in Myxedema: Explanation of "Brightly Icteric Tint," J. Clin. Endocrinol. 2: 33-35, 1932.

<sup>1235</sup>Mandelbaum, T. Cameli, S. and Milman, S.: Hypothyroidism, Hypertipemia and Carotenemia, J. Clin. Endocrinol. 2: 465-467, 1932.

extremities where it is sometimes combined with acrocyanosis and associated complications like chilblains and tuberculids.<sup>1327</sup> Several authors<sup>1328,1329</sup> saw deep ulcerations of the legs connected with hypothyroidism and they advised treatment with thyroid by mouth and thyroid powder or thyroid salve locally. The skin is dry especially on the extensor surfaces of the extremities. In some cases of acquired myxedema marked keratosis palmaris and plantaris was observed and successfully treated with daily doses of 0.2 — 0.3 Gm. of thyroid.<sup>13,1333,1340,1341</sup> The basal metabolism has often been studied in congenital ichthyosis. The findings and the results of thyroid therapy are controversial.<sup>1342-1344</sup>

The dryness of the palms and arm pits (anhidrosis) is striking since the secretion of the sweat glands and of the sebaceous glands is reduced or completely absent. Nevi and moles may appear and desquamation is pronounced due to the dryness and to the tendency toward increased keratosis. In advanced or neglected cases this may cause a picture similar to ichthyosis particularly around the knees and elbows and also in the axillary and inguinal folds (Reuter in discussion to Cornbleet and Cohen<sup>1345</sup>). In some cases of congenital ichthyosis thyroid therapy seems to have given relief.<sup>1346-1348</sup> Itching is a frequent complaint.

The edema in fully developed myxedema is nonpitting and firm. It is most marked in the face and in the ears which sometimes have a cauliflower like appearance.<sup>1349</sup> The facial features are coarse. The term *oedimo face*<sup>1350</sup> is significant. Eyes and nose appear smaller than normal the latter especially in children is saddle shaped. This sign is commonly met with. The eyelids especially the lower lids the skin of the forehead the ears and the lips are swollen and cause a deepening of the nasolabial and forehead folds. The suprastavicular fossae and the dorsa of the hands and feet are other sites of increased myxedematous or fat pads. The swelling may extend to the mucosae. The tongue the uvula and the nasal and laryngeal mucosae may become involved with a consequent disturbance of the voice. The thick protruding tongue of the cretin is a familiar picture.

<sup>1327</sup>Cornbleet and Dejanaro. Tuberculids and Hypothyroidism, *Acta dermo-sif* 23: 45, 1931. *Ebl* 3: 359.

<sup>1328</sup>Cohen S. H. Leg Ulcers Due to Thyroid Dysfunction, *J A M A* 102: 232-235, 1934.

<sup>1329</sup>Eppinger H. Thyroide H. stromschwäche als Symptom eines lokalen Myxödems, *Klin Wchnsch* 10: 643-643, 1931.

<sup>1330</sup>Meunier Fournier J. C. Kératodermie plantaire et palmaire chez une hypothyroïdienne. Sa guérison par la thyroïdine, *Bull et mèm. Soc. méd. d. Hôp. d. Paris*, 48: 1326-1327, 1932.

<sup>1331</sup>Cervino, J. M. Vertolini, A. and Larrosa Helgoers, R. A. Keratodermas of Hands and Feet and Thyroid Deficiency. *Endocrinology* 23: 618, 1934.

<sup>1332</sup>Krug M. and With, G. O. The Standard Metabolism I. Ichthyosis, *Acta dermat.-venereol.* 3: 543-552. *Ebl* 9: 403.

<sup>1333</sup>Slenczko, H. W. U. Untersuchungen über d. Stoffwechsel Ichthyotischer. *Arch. f. Dermat. & Syph* 159: 466-478, 1923.

<sup>1334</sup>Porter A. Basal Metabolism I. Ichthyosis, *Brit. J. Dermat.* 36: 478-491, 1936.

<sup>1335</sup>Cornbleet, Th. and Cohen, D. Pellagra and Myxedema, *Arch. Dermat. & Syph* 42: 1140, 1940.

<sup>1336</sup>Alten H. Ichthyosis als Folge endokriner Störung, *Dermat. Wchnsch* 81: 710-712, 1913.

<sup>1337</sup>Deereb, O. and Neuhäse, O. Myxödem und Ichthyosis. *München. med. Wchnsch* 76: 1464, 1929.

<sup>1338</sup>Idemose S. Ichthyosis simplex, *J. p. J. Dermat. & Urol* 34: 107, 1934.

<sup>1339</sup>Fraser, E. Ein Fall von chronischer Inflammation der Thyreoidea. Ein Beitrag zur Pathologie des Ödems, *Österr. dermat.* 23: 233-241, 1931. *Ebl* 29: 72.

Increased pigmentation especially on the forehead around the lids and some distance from the mouth occurs. Severe bronze-colored pigmentation of the body has been observed in cachexia thyroopriva.<sup>1281</sup> However it is doubtful whether or not the pigmentary changes are caused by the hypothyroidism. Curschmann<sup>1282</sup> infrequently found grey hair in adult patients. He relates this finding to his observation that adult patients with chronic myxedema due to their lowered metabolism, age later than normal persons. This author found patients with compensated myxedema at the age of sixty and seventy years look like forty five. Other authors frequently found premature greyness in myxedema.

Loss of hair is common in hypothyroidism. This clinical observation is supported by observations on thyroidectomized animals. The hair in myxedematous patients is dull dry brittle and easily wears off and sheds. The axillary and pubic hair becomes scanty or absent.<sup>1283</sup> The margins of the scalp tend to become bald. Bald spots not always of the common areata type occur and may respond well to thyroid therapy although this treatment is ineffective in the majority of the cases of alopecia areata. In women baldness of the forehead is sometimes striking.

The significance of the loss of hair of the lateral third of the eyebrows as a symptom of hypothyroidism especially in children (Hertoghe's or Levy and Rothschild's sign) is not generally recognized. It is less pronounced in the Teutonic races with whom thinner eyebrows are considered normal.

In some cases of hypothyroid infantilism the lanugo hair persists in considerable strength but disappears with thyroid medication.<sup>1284</sup>

The nails are often changed. Dystrophies have been found in some series up to 93 per cent.<sup>1285</sup> The size can be decreased the normal curvature absent and the nail may be very thin. Decrease in size brittleness, longitudinal and transverse grooving defective lunulae and white spots in the matrix are common.<sup>1286</sup> The rate of growth is markedly reduced.<sup>1287</sup>

The resistance to pyogenic infections blepharitis and erysipelas is low in myxedematous patients. The clinical appearance of the myxedematous skin is the result of edema and excess mucin in the epidermis degeneration of the collagen and elastic fibers and a sparse cellular infiltration about the vessels.<sup>1288</sup> The electric resistance of the myxedematous skin is increased.<sup>1289</sup>

### Circumscribed Myxedema

This not extremely rare condition is a paradoxical one (Trotter in discussion to Freudenthal<sup>1290</sup>). It consists of pretibial circumscribed lesions which are

<sup>1281</sup>Korber, A. Die Pathologie der Schilddrüse XXIII. Oester. Ges. Med. Wiesbaden, pp. 149-157, 1904.

<sup>1282</sup>Curschmann, H. Zur Klinik und Pathophysiologie des Myxedems (insbesondere der gutartigen Inkompletten Formen). Deutsche Zeitschr. f. Nervenk. 96, 28, 827.

<sup>1283</sup>Barrett, A. M. Hereditary Occurrence of Hypothyroidism With Dystrophies of the Nails and Hair. Arch. Neurol. & Psychiat. 2: 828, 1918.

<sup>1284</sup>Reuter, H. J. Histopathology of the Skin in Myxedema. Arch. Derm. & Syph. 24, 53, 1931.

<sup>1285</sup>Freudenthal, W. and Brillbauer, H. H. Myxedema papulosum et annulare. Proc. Roy. Soc. Med. 35: 244-260, 1942.



myxedematous in appearance and histology but are in the majority of the cases associated with hyperthyroidism even with the fully developed syndrome of exophthalmic goiter. It seems as if in these cases some parts of the skin especially of the lower legs are unable to use the hormone which is offered in abundance.



Fig. 174



Fig. 175

Fig. 174—Circumscribed herma myxedema. (Courtesy Division of Dermatology Department of Medicine University of Chicago.)

Fig. 175—Myxedematous herma. (Courtesy Dr. M. Jenner.)

The lesions are hard nodules or tuberous plaques of varying size sometimes covering both pretibial area. They are asymmetrical and may be normal in color yellowish pinkish or brownish. Inflammatory symptoms are mostly absent. The follicles are often dilated so that a pig skin or orange peel appearance result. The lesions are quite hard and nonpitting. Hypertrichosis within the lesion is another paradoxical feature which has been encountered.<sup>124</sup> The sweat secretion within the myxedematous lesion normal or absent.<sup>125</sup> The temper-

<sup>124</sup>Richer, W. Lokales System mit H. peritrichosis symmetrisch befallen (erschien in der Krankheitsgeschichte). Zbl. 42 871 1912.

<sup>125</sup>Jordan, J. T. Circumscribed myxedema Associated With Hypertrichosis. New York La. med. 18 10- 1912 Zbl. 11 756 1932.

ture may be much lower than in the normal skin.<sup>128</sup> On puncture a mucilaginous tenacious serum seeps from the wound. The microscope shows infiltration with masses and strands of mucin.

The major changes are found in the cutis. The connective tissue fibers are edematous and homogenized. Oval and stellate cells are scattered throughout.<sup>128, 129, 130</sup> Treatment with thyroid or iodine has occasionally produced toxic symptoms. Thyroidectomy precipitated the outbreak of circumscribed myxedema in some cases but abolished it in others. Since this dermatosis causes little discomfort, the treatment should be guided by the necessities of the general condition.<sup>128</sup>



Fig. 176. Myxedema, brownish, in patient with hyperthyroidism. From Atkinson J. O. Arch. Dermat. & Syph. 1941.

Lichenoid umbilicated papula,<sup>131</sup> tuberous plaque-like and other varieties of discrete myxedema are known as the atypical myxedema of Jadassohn and Doesecker.<sup>132</sup> The connection with thyroid dysfunction is usually less obvious.

<sup>128</sup>Carell W. L. L. Atypical Myxedema. Nederl. Tijdschr. geneeskd. 75: 4156-4159, 1931. Ed. 29: 743.

<sup>129</sup>O'Leary A. Localized Nodular Edema of the Extremities in Association With Exophthalmic Goiter. Arch. Dermat. & Syph. 21: 770, 1930.

<sup>130</sup>O'Leary E. A. Nodular Edema of the Face. Arch. Dermat. & Syph. 21: 330-331, 1930.

<sup>131</sup>Jadassohn F. Exophthalmic Goiter and Myxedema. Endocrinology 12: 43-5, 1924.

<sup>132</sup>Doesecker W. A. Relation between Myxedema. Arch. f. Dermat. & Syph. 22: 78, 1916.

in this group than in diffuse or pretibial myxedema.<sup>1285</sup> The oral mucosa may be involved.<sup>1286</sup>

Temporary facial puffiness following subtotal thyroidectomy but different from the localized form of myxedema has been observed in nine cases.<sup>1287</sup> It seems to be a mild form of myxedema and responds to thyroid therapy.

### The Parathyroid Glands

The hormone of the parathyroid glands is concerned with calcium metabolism. It maintains the level of ionized calcium in the blood and regulates the use of calcium for skeletal growth. The proper degree of nervous and muscular irritability and the viscosity and coagulation of the blood are also influenced by the presence of calcium.

Relations between the parathyroids and certain dermatoses have often been suspected (see scleroderma calcinosis) but our knowledge of the skin in hyperparathyroidism is meager and uncertain. Albright<sup>1288</sup> in his work on hyperparathyroidism does not mention any skin changes and no mention is made in the review of 135 proven cases by Wilder and Howell.<sup>1289</sup>

### Hypoparathyroidism

Extirpation of the parathyroids was in a number of cases followed by the outbreak of a severe and characteristic dermatosis clinically identical with impetigo herpetiformis (Hebra). Since other symptoms of insufficient parathyroid activity, especially tetany, have been found in spontaneous cases of impetigo herpetiformis, it seems justified to regard this disease as a dermadrome of hypoparathyroidism.

**Impetigo Herpetiformis—Hebra**<sup>1290</sup> in 1872 and shortly after him Kaposi<sup>1291</sup> first described the clinical picture of this disease and it has been but little changed since. The dermatosis starts with crops of pustules which often appear during pregnancy but sometimes in women without relation to pregnancy or in men. The primary lesion is a true pustule, i.e. a vesicle filled with pus from the beginning and has a red and swollen base. These pustules are the size of a pinhead and are superficially seated in the epidermis, being grouped in clusters and lines. Confluent pustules in the center of such groups form a scab (impetigo) while new pustules develop at the periphery and the center heals under the scab forming rings and polycyclic figures.

These eruptions may cover large areas, sometimes the whole body surface. The navel, the genital and inguinal areas, the armpits and the submammary

<sup>1285</sup>Thompson and Thompson: Temporary Edema of the Face Following Treatment for Euthyroidism. *Am. J. M. Sc.* 578: 73, 1929.

<sup>1286</sup>Albright, F., A. b. J. C. and Bauer, W.: Hyperparathyroidism. *J. A. M. A.* 192: 1275-1287, 1934.

<sup>1287</sup>Wilder, R. M. and Howell, L. P.: Etiology and Diagnosis in Hyperparathyroidism: A Review of 135 Proven Cases. *J. A. M. A.* 100: 427-431, 1930.

<sup>1288</sup>Hebra, F.: Ueber einige in der Schwangerschaft und bei Uterinkrankheiten der Frau beobachtete Hautkrankheiten. *Wien. med. Wchnschr.* 1872.

<sup>1289</sup>Kaposi, M.: Impetigo herpetiformis. *Arch. f. Dermat. & Syph.* 19: 273-295, 1887.

regions are usually first and most severely involved. Deep ulceration has not been seen. Sometimes the mucosa shows lesions analogous to those of the skin. Crops of new pustules are often accompanied by chills and fever. Nephritis, splenomegaly and cachexia are the rule in fully developed cases which may take on the aspect of generalized exfoliative dermatitis. Itching is not a dominant symptom.

Impetigo herpetiformis is a severe and often fatal disease. Of the thirteen patients with impetigo herpetiformis reported by Kaposi<sup>1267</sup> from 1872 to 1884 twelve died from the disease. Glävecke<sup>1268</sup> (1896) found a mortality of 80 per cent among 20 cases from the literature. During the last twenty years relatively many nonfatal cases have been reported.

This disease is so rare that many dermatologists have never seen it. The great interest which it aroused is due to the fact that it is a characteristic dermatosis with a definite endocrine relationship. Hebra<sup>1269</sup> and Kaposi<sup>1267</sup> who saw more cases than any other writers were convinced that impetigo herpetiformis is a disease of pregnant women. Later on Kaposi described a case in a man and more recently several cases in nonpregnant women. In children and in men<sup>1270</sup> have been presented.

In 1921 Schardorn<sup>1271</sup> reported two cases of impetigo herpetiformis and tetany in nonpregnant women who only three days before had been subjected to thyroidectomy. Both women died and at autopsy no parathyroids were found. If there was any doubt about the part the operation played in the etiology it has been removed by the publication of at least nine more cases following thyroidectomy<sup>1272-1275</sup>. In a case published by Kollisch<sup>1276</sup> tetany followed thyroidectomy. The patient later became pregnant and developed impetigo herpetiformis. On the other hand it is surprising that impetigo herpetiformis has not been seen more often among the many cases of total thyroidectomy. Hoehner<sup>1277</sup> e.g. in his famous paper in 1906 does not mention impetigo herpetiformis as a symptom of cachexia following total strumectomy.

The spontaneous cases in pregnancy are often but not always associated with symptoms of hypoparathyroidism. Osteomalacia, tetany<sup>1278-1282</sup> low

<sup>1266</sup>Gilbert. Impetigo herpetiformis. Arch. f. Gynäk. 82: 15-34 1898.

<sup>1267</sup>Kaposi A. F. Impetigo herpetiformis in Male. Arch. Dermat. & Syph. 29: 107-12, 1844.

<sup>1268</sup>Glävecke. Impetigo herpetiformis. Arch. f. Dermat. & Syph. 192: 108-130, 1901.

<sup>1269</sup>Hebra. Impetigo herpetiformis. Derm. Zeitschr. 53: 394-400, 1823.

<sup>1270</sup>Kapp. Dermatitis para hyperph. unter dem Bilde der Impetigo herpetiformis. Zbl. 29: 132, 1931.

<sup>1271</sup>Schardorn. J. Zur histologischen Therapie der Impetigo herpetiformis. Arch. f. Dermat. & Syph. 175: 83-105, 1927.

<sup>1272</sup>Wine. F. Dermatitis herpetiformis Appearing Three Weeks After Thyroidectomy. Arch. Dermat. & Syph. 37: 377-379, 1923.

<sup>1273</sup>Schmidt-Ladouce. Impetigo Herpetiformis and Cure With A. T. 1. (Dihydroxyacetone). Hbta. Med. Klin. 23: 1800 1927.

<sup>1274</sup>Schubert. M. Impetigo Herpetiformis. A. T. 10 Therapie. Derm. Wochenschr. 192: 76 1928.

<sup>1275</sup>Dankert. E. Impetigo herpetiformis, postoperative Tetanie, parathyreoprive Cachexie. Frankfurt. Zeitschr. f. Path. 26: 299 1929.

<sup>1276</sup>Kollisch. A. Leber Impetigo herpetiformis. Hbta. Arch. f. Dermat. & Syph. 187: 214-223 1929.

<sup>1277</sup>Kocher. K. Impetigo herpetiformis. Zbl. f. Gyn. 48: No. 22.

<sup>1278</sup>Kaplan. Leber Impetigo herpetiformis und Schwangerschaft. Zbl. 21: 2 9 1924.

<sup>1279</sup>Levinsky. Impetigo herpetiformis. Zbl. 48: 210 1923.

serum calcium<sup>1263-1265</sup> and cataract<sup>1262</sup> have been observed with impetigo herpetiformis in pregnancy but a considerable number of cases have been found free of all such symptoms. This together with the nonobligatory occurrence after parathyroidectomy suggests that hypoparathyroidism is only one of the pathogenetic factors. In which direction other factors may be sought is indicated by cases with pituitary findings,<sup>1264, 1270</sup> mediastinal tumor<sup>1266</sup> and dysfunction of the ovaries.<sup>1271</sup> The possibility of an infection which only develops under certain circumstances cannot be denied though the lesions and the blood have almost always been found sterile. Italian authors have lately suggested a virus infection



Fig. 177. Female aged 31 years. Widespread infection of skin hands feet and areas with vesicular lesions in case of many bile renal cataract and hypertension. (Courtesy Wiesbaden General Hospital.)

under certain hormonal and toxic conditions.<sup>1268</sup> The clinical similarity to pustular psoriasis must be mentioned since hypocalcemia seems to be an etiological factor in this dermatosis also.

The impetigo herpetiformis of pregnancy brings up the question of the artificial termination of the pregnancy in the case of this disease. Several dermatologists feel that this procedure is justified. However the disease not infre-

<sup>1263</sup> Carter E. and Pearse E. L. Impetigo Herpetiformis Occurring During Pregnancy. *Am J Obst & Gynec* 23: 14, 1937.

<sup>1264</sup> Korbe A. G. Hypocalcemia. *Arch f Derna Syph* 179: 322-31, 1929-1930.

<sup>1265</sup> Tryb A. Beitrag zur Ätiologie der Impetigo herpetiformis. *Arch f Derna Syph* 182: 407-411, 1921.

<sup>1266</sup> Bensch A. Impetigo herpetiformis. *Zbl B* 25: 51, 1924.

<sup>1267</sup> Bensch A. Impetigo herpetiformisähnliche Hautaffektion bei Iodintoxikation. *Arch f Derna Syph* 178: 623-624, 1924.

<sup>1268</sup> Zocchi. Impetigo herpetiformis in gra blauen Glomerulonephritis. *S* 465, 1939.

quently starts in the later months of pregnancy when inducing labor in the presence of a widespread purulent skin infection is a dangerous procedure. Moreover the termination of pregnancy does not always influence the course favorably. In some cases the patients died from the dermatosis during the puerperium. Nevertheless, if the diagnosis is made early the pregnancy should be terminated and future pregnancies prevented.<sup>1235,1236</sup>

There have been almost as many methods of treatment tried as cases recorded. Blood transfusions,<sup>1237</sup> injections of normal serum and of serum of normal pregnant women,<sup>1238-1241</sup> estrogenic hormone (Buschke) and X ray sterilization<sup>1242</sup> have been used. Sulfanilamide accomplished a spectacular recovery in one recent case.<sup>1243</sup> Calcium in large doses<sup>1244</sup> should always be given. In tetany Sevrunghaus<sup>1245</sup> advises the oral administration of a 35 per cent solution of calcium chloride in a sweet vehicle one to two teaspoonfuls three times daily. The medicine is given one-half hour before meals with plenty of water. Parathyroid extracts are unreliable. Dihydrotachysterol<sup>1246</sup> a derivative of ergosterol also known as A.T. 10 is more promising. There are a number of favorable reports on record.<sup>1247-1251,1253-1255</sup> The dose is five to twenty drops of the oily solution daily.<sup>1248</sup> A.T. 10 is so far the best substitute for the parathyroid hormone. It increases the phosphorus excretion and raises the calcium level of the blood.

Parathyroid insufficiency seems to increase the susceptibility to chronic *monilia* infections of the hands and nails.<sup>1256</sup>

Brittleness of the nails and hairs together with hyperhidrosis and Addisonoid hyperpigmentation is occasionally associated with hypoparathyroidism.<sup>1257</sup>

## The Thymus

Status thymicolymphaticus of the adult is a much disputed condition. The beard and body hair has been described as scanty and there often is a female configuration in men.<sup>1258</sup> Scantiness of the beard and of the axillary and pubic hair in both sexes with heterosexual distribution is part of Timme's syndrome which is a chronic multiglandular benign condition with pituitary gigantism, low blood pressure, low blood sugar and other features.<sup>1259</sup>

<sup>1235</sup>Buschke A. and Cuth W. Die Bedeutung der Gravitätserkrankungen für die künstliche Unterbrechung der Schwangerschaft. *München med. Wchnschr.* 76: 361-364, 1929.

<sup>1236</sup>Arborelius H. Zur Behandlung der Impetigo herpetiformis der verschiedenen Pemphigiformen und anderer sehr schwerer Hauterkrankungen mit Impetigo herpetiformis. *Abstr. Dermatol. Kongress Wien med. Wchnschr.* 80: 717-720, 780-782, 801-809, 1930.

<sup>1237</sup>Kotane Impetigo herpetiformis. *Zbl.* 25: 34.

<sup>1238</sup>Kotane P. L. X-ray therapy on Impetigo herpetiformis. *Dermat. Wchnschr.* 81: 1038-1052, 1930.

<sup>1239</sup>Grütz Impetigo herpetiformis. *Zbl.* 30: 719.

<sup>1240</sup>Frank L. J. Impetigo Herpetiformis. *Arch. Dermat. & Syph.* 58: 252-254, 1930.

<sup>1241</sup>Hell F. Schwere Schilddrüsenerkrankungen. *Deutsche med. Wchnschr.* 55: 730-732, 1930.

<sup>1242</sup>Arborelius H. In: Kibicki, and *etiology of the Impetigo herpetiformis*, Wien med. Wchnschr.

80: 127, 1930.

<sup>1243</sup>Wojcik A. Albrecht F. and McCune D. J. Five Cases (Three in Adults) of Idiopathic Hypoparathyroidism Associated With Nodules. *J. Clin. Endocrinol.* 3: 625-634, 1913.

<sup>1244</sup>Emerson H. Status Lymphaticus in Adults. *Arch. J. Med.* 23: 109, 1914.

<sup>1245</sup>Walf W. *Endocrinology in Modern Practice*. Philadelphia, 1936, W. B. Saunders Company.

Carcinoma of the thymus has been seen to produce Cushing's syndrome in at least 3 cases.<sup>1291-1292</sup> The juvenile Hercules syndrome of precocious puberty in the male was seen in a case of mediastinal tumor probably a thymus lesion.<sup>1292</sup> Most thymomas do not provoke dermadromes.

Deficiency of the thymus has by several authors been thought to be a cause of *psoriasis*. The hypothesis was based on therapeutic results with injections of thymus extract<sup>1293</sup> and stimulating doses of roentgen radiation directed to the upper sternal region.<sup>1294-295</sup> Little has been heard of the subject during the last fifteen years.

<sup>1291</sup>Leyton, H. Turnbull, H. M. and Bratton A. H. Primary Cancer of the Thymus With Paraglandular Disturbance. *J. Path. & Bact.* 34: 635, 1931.

<sup>1292</sup>Duguid, J. B. and Kennedy A. M. Oat-cell Tumors of Mediastinal Glands, *J. Path. & Bact.* 23: 83, 1930.

<sup>1293</sup>Thompson K. W. and Kleinhardt L. Cushing Syndrome. *J. Clin. Endocrinol.* 3: 445-452, 1943.

<sup>1294</sup>Weber E. P. and Wohl, M. Macrogenic osoma: A Juvenile Hercules Type With Tumor in Superior Mediastinum, *M. Press* 211: 23-28, 1944.

<sup>1295</sup>Samberger J. Ueber das Wesen der Psoriasis. *Acta dermat. venerol.* 2: 359, 1921.

<sup>1296</sup>Brock, W. Beziehungen der inneren Sekretion zur Schuppenflechte und deren Behandlung mit Thymusbestrahlung, *Strahlentherapie* 11: 593-604, 1930.

<sup>1297</sup>Brock W. Psoriasis and Internal Secretion, *Deutsche med. Wochenschr.* 67: 1420-1422, 1921.

## CHAPTER XVIII

# DISORDERS OF THE ENDOCRINE GLANDS

## THE ADRENAL GLANDS

The adrenal cortex through its hormone cortin is concerned with water, mineral and carbohydrate metabolism<sup>1396</sup>. It keeps up the muscular strength and it has important functions in pregnancy and lactation. Androgenic substances which are able to masculinize the appearance of females are produced in the adrenal cortex or in its neoplasmas. The medulla of the adrenal glands produces adrenalin which besides other effects stimulates the sympathetic system and inhibits the vagus. Destruction of the adrenals is fatal.

### Addison's Disease

Addison's disease<sup>1397</sup> starts insidiously usually in middle life. Progressive asthenia and muscular fatigability, hypotension, epigastric pain, anorexia, morning sickness and other gastrointestinal symptoms may after long periods of relative mildness, suddenly increase and give rise to an acute condition known as Addisonian crisis. Hyperpigmentation of the skin is an outstanding symptom. Dehydration, decrease in the sodium and chlorine concentration in the blood, increase in the blood potassium and nonprotein nitrogen (urea) and hypoglycemia are important findings especially during the crisis. The urinary sodium chloride is high. Sugar may occur in the urine in spite of the hypoglycemia<sup>1398</sup>. The blood viscosity is high. Anemia is marked. The elimination of water after a sudden large intake of water is delayed. A water test designed by Robinson, Power and Kepler<sup>1399</sup> together with blood and urine chemistry has lately been shown to be of great diagnostic value<sup>1400</sup>. The course is almost always fatal but with modern treatment health may be restored to such a large measure that cure may seem to be accomplished yet sudden death may occur from trivial causes<sup>141</sup>. The cause of the syndrome is destruction of the adrenal cortex due in 9 out of 10 cases, to tuberculosis.

<sup>1396</sup>Goldberger M. A. The Adrenal Glands in Health and Disease. Philadelphia, 1944. F. A. Davis Company.

<sup>1397</sup>Addison T. A Collection of the Published Writings of the Late Thomas Addison on the Constitutional and Local Effects of Disease of the Suprarenal Capsules. New Sydenham Society 1859. Reprinted in Rowntree and Peel. Addison's Disease. Philadelphia, 1931. W. B. Saunders Company.

<sup>1398</sup>Robinson, F. J., Power M. H. and Kepler E. J. Addison's Disease—Diagnosis. Proc. Staff Meet. N. Y. Clin. 16: 877-883, 1941.

<sup>1399</sup>Kepler E. J., Power M. H. and Wilder R. M. Concentrations of Chloride, Sodium and Potassium in Urine and Blood: Their Diagnostic Significance in Addison's Disease. J.A.M.A. 111: 117-122, 1938.

<sup>1400</sup>Rosenfeld, L. G. Report of 3 Cases of "Clinical" Addison's Disease Surviving More Than 18 Years. Endocrinology 28: 793-800, 1947.



Carcinoma of the thymus has been seen to produce Cushing's syndrome in at least 3 cases.<sup>1299-1300</sup> The juvenile Hercules syndrome of precocious puberty in the male was seen in a case of mediastinal tumor probably a thymus lesion.<sup>1301</sup> Most thymomas do not provoke dermadromes.

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<sup>1299</sup>Leyton, O. Turnbull, H. M. and Bra ton, A. B. Primary C over of the Thymus With Paraganglionic Disturbance. *J. Path. & Bact.* 34: 635, 1931.

<sup>1300</sup>Dravid, J. B. and Kennedy, A. M. Oat-cell Tumors of Mediastinal Glands, *J. Path. & Bact.* 23: 23, 1930.

<sup>1301</sup>Thompson, K. W. and Essekhardt, L. Cushing Syndrome. *J. Clin. Endocrinol.* 3: 445-452, 1943.

<sup>1302</sup>Weber, E. P. and W. H. M. Macrogonadism of Juvenile Hercules Type With Tumor of Superior Mediastinum, *M. Press* 231: 23-36, 1944.

<sup>1303</sup>Samborger, J. Ueber das Wesen der Psoriasis. *Acta dermat. venerol.* 2: 339, 1921.

<sup>1304</sup>Brock, W. Beziehungen der inneren Sekretion zur Schuppenflechte und deren Behandlung mit Thymusbestrahlung, *Strahlentherapie* 11: 363-404, 1930.

<sup>1305</sup>Droch, W. Psoriasis und innere Sekretion, *Deutsche med. Wochschr.* 67: 1420-1422, 1921.

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#### THE ADRENAL GLANDS

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<sup>1346</sup>Goldschaber M. A. The Adrenal Glands in Health and Disease. Philadelphia, 1944. F. A. Davis Company.

<sup>1347</sup>Addison, T. A Collection of the Published Writings of the Late Thomas Addison on the Constitutional and Local Effects of Disease of the Suprarenal Capsules. New Sydenham Society 1859. Reprinted in Ben. tree and Small. Addison's Disease, Philadelphia, 1931. W. B. Saunders Company.

<sup>1348</sup>Erdmann, F. J. Power M. H. and Kepler E. J. Addison's Disease—Diagnosis. Proc. Staff. Meet. Mayo Clin. 16: 877-883. 1911.

<sup>1349</sup>Cutler M. H. Power M. H. and Widdow R. M. Concentrations of Chloride Sodium and Potassium in Urine and Blood. Their Diagnostic Significance in Addison's Disease. J.A.M.A. 111: 117-123. 1933.

<sup>1350</sup>Rowntree L. B. Report of 3 Cases of "Clinical" Addison's Disease Surviving More Than 14 Years. Endocrinology 26: 793-800, 1940.



Fig. 178.—Addison disease. Patient (left) with her sister for comparison. Discoloration only complaint so far. Patient died five months later.



Fig. 179.—Addison disease. Note pigmentation of exposed part. (Courtesy Wisconsin General Hospital.)

**Dermadromes.**—*Hyperpigmentation* of the skin in connection with destructive adrenal disease is in the vast majority of cases an early symptom often appearing before asthenia and fatigability. Pigmentation about the knuckles may be the first manifestation <sup>1912</sup>1913.

The fully developed discoloration is uneven in distribution and color. The face, neck, hands and other light exposed parts, the normally pigmented areas, the nipples, the linea alba of women who have been pregnant, the genital region, the gluteal fold and the umbilicus are usually affected first. All areas subject to



FIG. 90.—Addison's disease. Net pigmentation in heli area and over prominent bones. (Courtesy, Wisconsin General Hospital.)

pressure, friction and irritation are apt to take on a darker color than the rest of the skin. Thus girdles, garters, shoulder straps, collars, collar buttons and bandages may leave indelible marks. The author saw a deaf woman who was wearing a hearing aid apparatus, the cord of which ran along her back. The slight pressure and friction of this cord had left a deep pigmented mark in the skin at a time when there was hardly any asthenia and little other pigmentation. The creases of the palms and the wrists are sharp dark lines, while the palms themselves are still light. Tight skin over bones is often hyperpigmented. Scars, e.g., vaccination marks, have a pronounced tendency to darken early in Addison's

<sup>1912</sup>Rowatree, L. O. and Neff, A. M. A Clinical Study of Addison's Disease. Philadelphia, 1921. W. B. Saunders Company, p. 176.  
<sup>1913</sup>Neff, A. M. and Rowatree, L. O. Addison's Disease With Anomalous Pigmentation. Endocrinology 8: 262, 1929.

Fig. 181.



Fig. 182.

Fig. 181 Addison disease. Pigmentation of palmar creases

Fig. 182—Addison disease. Pigmentation of scars (Not from scars)

disease. Spillmann<sup>133</sup> advises to watch for the development of pigmentation after the application of an irritant plaster of mustard seed. Besides the unevenness caused by the various traumas, great differences in the intensity of the pigmentation occur. In some cases the discoloration is blotchy, in others irregular and ill defined. Some cases present patterns which look like a geographical map, especially if much depigmentation accompanies the pigment increase. Thus pictures resembling vitiligo may ensue. True vitiligo has often been seen together with Addison's disease<sup>134</sup> and it is interesting that hypotension has been found in a number of vitiligo cases.



Fig. 183.—Addison's disease. Deep hyperpigmentation and depigmentation surround the mouth. White patient.

*Leukoderma acquisitum centrifugum* (Sutton's disease) and vitiligo have been seen in one case of Addison's syndrome.<sup>134</sup> Some areas of the skin offer a marked resistance to the pigmentation. The narrow strip surrounding the lips often stays pale even in extremely dark pigmented cases. The same is sometimes true of the fingertips and nailbeds and the backs of the hands, to a certain extent also of the eyelids. The circumoral strip often remains relatively white in other pigmentations as well, for example in the form of discoloration which has been described by Poor<sup>135</sup> as *chloasma periorale-irgnum*.

The color of the Addison melanoderma is most commonly a tan<sup>136</sup> but may vary from slate, amber or brown shades to the dark black of a full blooded Negro. This latter however is very rare. The depigmentation of the circum-

<sup>133</sup>Spillmann, L. *Dermatosen en rapport avec des troubles des glandes endocrines et de la nutrition*, Nouvelle Pratique Dermatologique, Vol. 2, Paris 1936, Masson & Cie pp. 544-731.

<sup>134</sup>Obermayer, M. E. *Leukoderma Acquisitum centrifugum and Vitiligo in Patients With Addison Disease*, Arch. Derm. & Syph. 35: 326, 1937.

## PLATE III

- 1 Addison disease. Advanced case
- 2 Addison disease. Pigmented palmar creases.
- 3 Addison disease. Pigmentation of the tongue.
- 4 Addison disease. Pigmentation of the gums.
- 5 Hemangioma of pregnancy: Recurring in several pregnancies and receding spontaneously after childbirth (Patient of Dr. J. Barrock.)
- 6 Erythrois vulva to lupic carcinomas.



PLATE III





FIG. 144.



FIG. 145.



FIG. 146.



FIG. 1 — Addison disease. Pigmentation of labial mucosa.

FIG. 145 — Facial pigmentation of oral mucosa.

FIG. 146 — Addison disease. Pigmented spot on gum.

oral area and of the nailbeds is most striking in such cases. Jet black freckles are often seen mainly in areas exposed to light but even in unusual places like the palms and soles.<sup>1211</sup>

The lips and the oral mucosa almost always show quite sharply outlined slate or bluish spots sometimes streaks. They resemble those seen in the mouth of the Negro. They appear rather early in the labial buccal or palatal mucosa sometimes on the tongue. The conjunctivae and the sclerae of the eyes as well as the vagina may participate in the general hyperpigmentation. Melanosis of the rectal mucosa has not yet been demonstrated. A number of cases of Addison's disease in the Negro have been recorded. Here the Addisonian pigment may be superimposed on the natural pigment so that the palms and soles become darker and an extremely dark color of the rest of the skin results.

Montgomery and O Leary<sup>1212</sup> emphasizes the relative softness of the skin which he relates to the flattening of the rete ridges and the thin but not atrophic epidermis. Sweating is often pronounced. Some believe the sweat to have a fishlike odor.<sup>1213</sup> In prolonged cases the hair may become darker particular coarseness or hypertrichosis is denied.<sup>1213</sup> Premature graying and scantiness of the hair has been observed in the course of the disease.<sup>1214 1217</sup> The frequent shedding of the axillary and pubic hair is emphasized by Albright.<sup>1218</sup> The nails may rarely take on a yellowish hue. Usually they stay pale.<sup>1214</sup>

**Histopathology and Pathogenesis**—The pigment is melanin and as such it is free of iron. It is accumulated in the tops of the basal cells of the epidermis. Dendritic chromatophores are also found in the cuts.<sup>1219</sup> Bittorf<sup>1220</sup> tried to explain the pigmentation in Addison's disease by assuming a higher oxidase content in the skin. His experiments with the skin of patients with Addison's disease were not confirmed by B. Bloch<sup>1221</sup> and his school who believed that not the increased oxidase content of the skin but an increased amount of melanogens accounts for higher melanin production. It was suggested that in the disturbed adrenals less tyrosin might be changed into adrenalin and thus more tyrosin might be available as a promelanin. Later (1928) Szent-Györgyi<sup>1222</sup> who isolated vitamin C from normal adrenals advanced the theory that the high reducing power of this substance (then called hexuronic acid) serves as a control in the oxidation of promelanin to melanin in the normal skin. Its deficiency caused by destruction of the cortex would increase the oxidizing power of the skin and thus enhance the melanin formation which is an oxidation process. A great deal of experimental work seems to corroborate the antipigmentogenic role of vitamin C.

<sup>1211</sup>Montgomery H., and O Leary P. A. Pigmentation of the Skin in Addison's Disease. *Acute Shock, Nigricans and Hemochromatosis*. Arch. Dermat. & Syph. 21: 970-984 1930.

<sup>1212</sup>Dauer Julius. Innere Sekretion. Berlin, 1937 Julius Springer.

<sup>1213</sup>MacBryde, C. M. Addison Disease. *M. Clin. North America* 28: 391-400, 1912.

<sup>1214</sup>Albright F. Smith, P. H. and Fraser R. Syndrome Characterized by Primary Ovarian Insufficiency and Decreased Stature. *Tr. A. Am. Physicians* 97: 219-226, 1912.

<sup>1215</sup>Bittorf. Pathologie der Nebennierenkrankheiten, Jena, 1909, G. Fischer. Ueber die Pigmentbildung bei der Addison'schen Krankheit. *München. med. Wchnschr.* 78: 370-372, 1923.

<sup>1216</sup>Bloch, B. and Löffler W. Untersuchungen über die Bronzefärbung der Haut bei der Addison'schen Krankheit. *Deutsches Arch. f. Klin. Med.* 111: 303-391 1917.

<sup>1217</sup>Szent-Györgyi A. Observations on Function of Peroxidase Systems and Chemistry of Adrenal Cortex. Description of New Carbohydrate Derivative. *Biochem. J.* 22: 1217-1209 1928; also On the Chemistry of the Adrenal Cortex. *Am. J. Physiol.* 99: 536 1932.

It is well known that lemon juice which has a high vitamin C content prevents the blackening of cut surfaces of fruit e.g. avocado pears and inhibits the oxidative dopa reaction.<sup>122</sup> Vitamin C is also able to bleach pigmentations including those of Addison's disease.

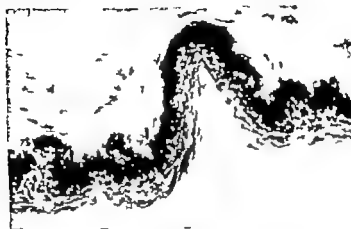


Fig. 187—Addison's disease. (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)

Pigmentation of the skin and melanogen formation in the urine after exposure to light can be inhibited by previous administration of vitamin C.<sup>123, 124</sup> W. Jadassohn and Schaaf<sup>125</sup> however showed that even large amounts of vitamin C could not prevent the pigmentation produced in guinea pigs by estrogens, and other authors<sup>126</sup> believed that the concentration of vitamin C in the human serum would not be strong enough to inactivate the dopa oxidase and to inhibit the dopa reaction as it does *in vitro*. In this connection the vitamin C deficiency in pregnancy which is a period of increased pigment formation may be mentioned.

The theory of the pigmentation inhibiting power of vitamin C would be in line with Hittorf's<sup>127</sup> opinion that it is the higher oxidizing power and not the higher amount of melanogen which causes the Addisonian pigmentation.

Szent Györgyi<sup>128</sup> in accordance with Bloch and Löffler's<sup>129</sup> work, tried to link the theories by suggesting that vitamin C deficiency which also leads to decreased production of adrenalin might thus keep more melanogen available for production of melanin. Adrenalin is closely related to several of the melanogens (pyrrol, tyrosin, dopa, etc.). If this double pigmentogenic role of vitamin C should be confirmed it might help to explain the high degrees of pigmentation reached in Addison's disease.

<sup>122</sup>Gepp, W., Kühn, J. and Schroeder H. Die Vitamine 24. Hefte, 1923. Ferdinand Enke.  
<sup>123</sup>Schade H. A. Beitrag zur Frage des Einflusses von Vitamin C (1-Ascorbinsäure) auf Pigmentierungsverläufe. Klin. Wochenschr. 10: 60-61, 1932.

<sup>124</sup>Kahler H. and La Crest, Y. Ueber den Einfluss der Ascorbinsäure auf die Melanogenabscheidung. Klin. Wochenschr. 10: 1831, 1832, 1932.

<sup>125</sup>Jadassohn, W. and Schaaf, F. Depigmentierende Wirkung der 1-Ascorbinsäure (Vitamin C). Klin. Wochenschr. 12: 813-816, 1934.

<sup>126</sup>Faill, P. and Fowler A. Vitamin C and Deparreaktion. Klin. Wochenschr. 14: 876-877, 1935.

Hyperpigmentation has been observed in true scurvy. This observation could be used as another argument in favor of the vitamin C theory of the Addisonian pigmentation. Difficult to reconcile with the outlined role of vitamin C is the observation that this substance occurs together with melanin in the human skin.<sup>1207</sup> Lately (Edelbacher and Zeller quoted by Robert and Zeller<sup>1215</sup>) the experimental formation of melanin from histamine by the enzyme diamine oxydase (DO) has opened a new path. In adrenalectomized animals the formation of the histamine decomposing enzyme DO is disturbed. But not more than this hint of a relationship has so far been given. A definite explanation of the pigmentation in Addison's disease has not yet been found.

Recently the role of the sympathetic system in the pigment formation in Addison's disease has again been emphasized.<sup>1209</sup> The disturbance of the sympathetic system caused by the destruction of the adrenal cortex may lead to melanoosis. Hyperpigmentation due to destruction of the plexus coeliacus and other sympathetic structures by neoplasms, aneurysms or injuries is well known.<sup>1204</sup> see also *acanthosis nigricans*, nervous system.

**Treatment**—The treatment of the pigmentation in Addison's disease has hardly been tried by other methods than those directed towards the adrenal insufficiency. Four important advances have been made during the last decade.<sup>1206</sup> These are (1) the introduction of salt therapy, (2) the restriction of potassium salts, (3) the elaboration of potent extracts of the adrenal cortex and (4) the synthesis and availability of desoxycorticosterone esters. It seems as was to be expected that their value is due to the fact that they maintain life, not that they cure the destructive process in the adrenal cortex, just as insulin does not cure diabetes. In spite of the sometimes dramatic effect on most of the symptoms,<sup>1201</sup> the fully developed pigmentation is hardly ever reversed. This opinion of investigators who treated many cases of Addison's disease is in contrast to other reports.<sup>1212-1222</sup> Dehydration in times of remission and while under treatment with desoxycorticosterone and salt may make the patient appear lighter in color. The pigmented spots in the mouth will rarely disappear under any form of treatment.<sup>1223</sup> In the rare cases of syphilitic Addison's disease complete disappearance of all symptoms including pigmentation has been seen. But unfortunately the vast majority of the cases of Addison's syndrome are due to tuberculosis.

Some metabolic parallels of adrenal insufficiency and pemphigus, especially the lowering of the chloride and protein level and the increase of the plasma volume and interstitial fluid have led to encouraging trials of desoxycorticosterone acetate

<sup>1207</sup>Cornbleet T. Vitamin C and Pheum. *Arch. Derm.* & Syph. 35: 471-479, 1937.

<sup>1208</sup>Robert F. and Zeller E. A. Pheum: Formation and Diamine Metabolism. Role of Diamine Oxidase. *Bch. et. med. W. kocher* 21: 1805-807, 1941.

<sup>1209</sup>Von K. p. T. Haut melanoosis ad Nebennieren. *Virchow. Arch. f. path. Anat.* 309: 311-317, 1943.

<sup>1210</sup>Loeb, R. F. *Adrenal Insufficiency*. Baill. New York Acad. Med. 11: 349-367, 1940.

<sup>1211</sup>Rowntree L. O. Results of Treatment of Addison Disease. *N. Clin. North America* 21: 1779-1787, 1940.

<sup>1212</sup>Edelbacher A. Pathologie et etiologie des melanoismes d' type addisonien. *Presse med.* 23: 291, 1921.

<sup>1213</sup>Loeb, R. F. *Adrenal Cortex Insufficiency*. J. A. M. A. 116: 2495-2500, 1941.

(docu) in pemphigus<sup>1224, 1225</sup> The recommended dose is 5 mg 3 times daily for 3 weeks and 5 mg daily thereafter. Autolytic findings of severe adrenal lesions in pemphigus have been reported by Goldziher<sup>1226</sup>

### Adrenal Tumors and Hyperplasias

Adrenal cortical tumors and hyperplasia of the adrenal cortex produce a syndrome which has received several names. Hirsutism<sup>967</sup> which refers to the main feature of hypertrichosis is most often used. Other terms are hyperadrenalism, genitosuprarenal syndrome and genitosuprarenal virilism. The term interrenalism<sup>1227, 1228</sup> refers to the interrenal organ of the elasmobranch fishes which instead of adrenals have an elongated body between the kidneys, closely resembling in its histology the mammalian adrenal cortex. Lately the syndrome of rapidly acquired obesity of the trunk, kyphosis and round shoulders, striae, dusky skin and hirsutism, amenorrhea or impotence, hypertension and fatigability has often been referred to as Cushing's syndrome<sup>1229</sup> even if it is not associated with Cushing's disease, basophil adenoma of the pituitary. Primary adrenal tumors of the cortex as well as of the medulla are very rare. Gibson<sup>1230</sup> found only one in approximately 12 000 admissions to the University of California Hospital.

The adrenal cortical tumors or hyperplasias which produce the syndrome of hirsutism occur in females in 80 per cent of the cases. A considerable number has been found in young children even in the newborn.<sup>1231</sup> The cortical neoplasms observed so far have been carcinomas, benign adenomas, sarcomas and metastatic growths from cancer of the breast or of the stomach. The localization in the cortex rather than in the medulla is more important in the production of a typical syndrome than the histology of the tumor. Very small adenomas may cause fully developed hirsutism. No parallelism exists between the size of the neoplasm and the degree of the syndrome. The hypernephromas (Crawitz tumors) do not cause hirsutism. In several instances highly malignant cortical neoplasms were found without having produced the syndrome of hirsutism<sup>1232</sup> (Wu quoted by Kepler and Keating<sup>1233</sup>).

**Dermadromes** — The syndrome caused by adrenal cortical tumors is modified by sex and age. In small boys precocious puberty with enlargement of the

<sup>1224</sup>Talbot, J. H., and Coombs F. S. Pemphigus, Arch. Dermat. & Syph. 41: 325-329, 1940.

<sup>1225</sup>Gekizian, A., Markham, M. J. and Schaffer, A. J. Case of Pemphigus Treated With Desoxy corticosterone Acetate. J. Clin. Endocrinol. 3: 342-344, 1942.

<sup>1226</sup>Goldziher, J. W. Adrenal Glands in Pemphigus Vulgaris, Arch. Dermat. & Syph. 52: 43-44, 1946.

<sup>1227</sup>Apert, E. Sur l'hirsutisme. Bull. et mem. Soc. med. d. Hôp. de Paris 45: 181, 1923.

<sup>1228</sup>Altkus, E. Über Androgensformen im Interrenalismus, Zentralbl. f. Gynäk. 89: 2: 20-24, 1912.

<sup>1229</sup>Wright, R. Applied Physiology. New York, 1940. Oxford University Press.

<sup>1230</sup>Watts, F. L. Estimation of Urinary ketosteroids in the Diagnosis of Adrenal Cortical Tumors, Cancer Research 4: 48-5, 1944.

<sup>1231</sup>Gibson, T. K. The Diagnosis of Adrenal Tumors With Classification of Adrenal Tumor Syndromes, Case, J. Urol. 35: 82-86, 1937.

<sup>1232</sup>Mayr, C. and Lang, F. J. Über Macromolekulare Interrenalis Congenita, Endokrinologie 14: 223, 1934.

<sup>1233</sup>Kepler, E. J. and Keating, F. R. J. Diseases of the Adrenal Glands. II. Tumors of the Adrenal Cortex. Diseases of the Adrenal Medulla and Allied Disturbances, Arch. Int. Med. 66: 1010-1026, 1941.

penis hypertrichosis and muscular development create the type known as the infant Hercules. Even paternity has been reported.<sup>134</sup> In adult males<sup>134</sup> gynecomastia feminine habitus disappearance of the beard and a decrease in the size of the penis and testes have been observed. Less than ten cases of this particular condition have been reported.<sup>136 138</sup> In small girls precocious puberty hypertrichosis obesity and virilism are the rule while in adult females amenorrhea and virilism dominate the syndrome. Sometimes even baldness of the male type and a mustache will develop. The breasts decrease in size. This group is the largest. But it must be kept in mind that these syndromes are not pathognomonic for adrenal cortical lesions alone. Similar changes have been seen in basophilic pituitary tumors various intracranial diseases hyperfunctioning gonadal tumors thymus tumor<sup>139</sup> and other rare conditions (see chapter on puberty).

*Hypertrichosis* is the outstanding dermatome in cortical tumors. It is an almost obligatory early conspicuous and sometimes even monstrous manifestation. However it is by no means diagnostic of adrenal cortical tumor. Not only does it occur in the above mentioned conditions but marked degrees of hypertrichosis are frequently seen in apparently healthy women with no symptoms of any endocrine disorder. (See also chapter on Pregnancy.) Hirsutism in children with adrenal cortical tumor has been observed as early as the first year of life even in the newborn. There are reports of young children with beards pubic and axillary hair and heavy and pigmented lanugo growth of girls of nine with bushy eyebrows and of boys of the same age who had to shave daily. The pubic hair growth in these cases usually resembles the male type. The pubic change may be unilateral.<sup>140</sup> High urinary androgen output has been observed.<sup>144</sup>

In adult women hirsutism can produce the most unusual pictures. You should be women and yet your beards forbid me to interpret that you are so

(Macbeth I 3) This best characterizes the impression one gets of some fully developed cases. Some of the 'bearded women' of the circus side shows belong to the adrenal group. The pubic hair changes to the male type. The lanugo becomes pigmented and in some parts of the body over an inch in length. Long pigmented hairs in the areolae of the nipples and coarse hair in the skin over the sternum and frequently on the mammae are conspicuous. Unusually long eye lashes have been seen.<sup>140</sup> In contrast to the general hirsutism is the loss of head hair in women with adrenal cortical tumor resembling the male baldness.<sup>134 138</sup>

<sup>134</sup>Looney J M: Sex Factors of the Adrenal Gland, Endocrinology 27 511-520 1940

<sup>136</sup>Kepler E F: The Adrenal Glands. Paper read before the Medical Society of Milwaukee County Nov 21 1939

<sup>138</sup>Hedl Caudaker: 3 m nliche F lle von N. beendr renr ndentumoren mit (hypertrichotischen) S dungen, Deutsche Zeitschr f. Chir 236 277 293, 1930.

<sup>140</sup>Rimell H W and Williams R H: Hirsutism in Females, Am. Fed. Ch. Research (1941) 1 25-30, 1944

<sup>142</sup>Dorfman R J Wilson H M and Peters J P: Differential Diagnosis of Basophilism (Cushing) and Allied Conditions. Cortical Tumors and Arrhenoblastomas, Endocrinology 27 1 15, 1940

<sup>144</sup>Reitter C: Ein Fall mit brennender Hitze, Zeitschr f. A. u. G. 72 8 7 1931

<sup>146</sup>Raber J:  berfunktion des grossen Nebennierensystems ohne anatomisches Defect, Wien. klin. Wochenschr 45: 552 556, 1930

Changes of the *pigmentation* in adrenal cortical tumors include occasional increased pigmentation around the nipple in adult males and in females pigmentation of the linea alba and the vulva comparable to that of pregnancy.

Unusual *acne* and comedos either in small children or in adults is almost invariably seen in cortical tumors.<sup>130</sup> The acne itself often seems to differ from the typical juvenile form and resemble the severe pyoderma type known as *acne conglobata*.<sup>131</sup>



Fig. 133 — Adrenal cortical carcinoma. Hyperpigmentation. (Courtesy Wisconsin General Hospital.)

The amazing symptoms of *precocious puberty* in adrenal cortical tumors have led to the publication of a great number of almost identical cases. Besides the hair changes which have already been mentioned, menstruation in early childhood and breast development have often been observed. Growth of the clitoris to an erect le penis with glans corona and a hypospadiac groove on the ventral surface with the labia minora shaped like a prepuce and the labia majora like a scrotum adds to the monstrosity of the syndrome. Such girls may have a deep voice. The whole body of these patients may show unusual growth with or without obesity and hirsutism. The infant Hercules, a "sturdy little man" with unusual muscular and intellectual development and with a large erect le penis is the rare counterpart in boys. The skin of the entire body is often mottled with dusky purplish red areas similar to cutis marmorata.<sup>132</sup> The features in precocious puberty are bloated, the complexion dusky and congested.

*Obesity* is not uncommon in cases of adrenal cortical tumor but it is more the distribution of the fat which is striking than the actual amount. The com-

<sup>130</sup> Kistler et al.: *O. The Adrenogenital Syndrome*. J. A. M. A. 116: 2679-2682, 1911.



bination of the full face the pad in the high dorsal region and the heavy abdomen together with the thin extremities creates a characteristic habitus.<sup>130</sup>

Next to the pituitary basophil adenoma cortical tumor of the adrenal is the condition which is most frequently connected with *Cushing's syndrome*.<sup>130</sup>

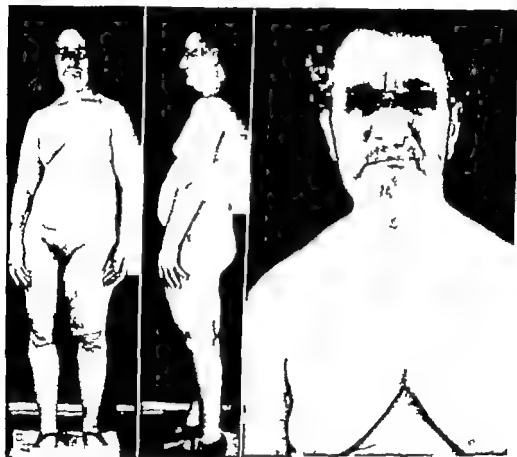


Fig. 100—Achard-Thiers' syndrome (diabetes in bearded women). (From Tollen, R. L. and Sedman, W. A. J. Clin. Endocrinol. Courtesy of Charles C. Thomas, Publisher Springfield, Ill.)

Some of the cases of so-called *diabetes of the bearded women*<sup>130</sup> belong here. In about 25 per cent of the reported cases hypertension amenorrhea obesity and acneiform eruptions have been noticed.<sup>144 145</sup>

<sup>130</sup>Achard Ch. and Thiers J. La triade phéocromine et son association à l'insuffisance stéroïdienne (diabète des femmes à barbe) Bull. Acad. de méd. Paris 90 51-60, 1921

<sup>144</sup>Shepardson H. C. and Shapiro E. Diabetes of Bearded Women, Endocrinology 24 237 252, 1939

The urinary output of androgens (17 ketosteroids) is often high in adrenal cortical tumors.<sup>1244,1264-1266</sup> There is a general tendency to interpret Cushing's syndrome with or without pituitary adenoma as caused by hyperadrenocorticalism.<sup>1267,1268</sup> Striae have been seen to appear after the injection of adrenal cortical extract. The diagnosis of adrenal cortical tumor is mostly suggested by the described symptoms. But however striking they are all or some may be absent and in spite of their presence no adrenocortical tumor may be found. The similarity of symptoms in other conditions has been mentioned. The roentgenographic demonstration of cortical lesions by air injection into the perirenal fascial spaces is possible but difficult and not without danger. In recent years estrogenic and androgenic substances substances which prolong survival of adrenalectomized animals and inactive substances which are chemically related to hormones have been found in the urine of patients with hyperfunctioning cortical lesions.<sup>1269,1270</sup> But these findings are no more constant than other signs and symptoms. Many of the organic changes even the monstrous symptoms of feminization and masculinization are reversible if the cortical tumor is removed. However since most of these neoplasms are malignant only few patients live long enough to experience the return of normalcy. No confirmed dermatomes have become known in tumors of the adrenal medulla.

<sup>1244</sup>Crooks, A. O. and Galloway, E. K. The Differential Diagnosis of Basophilism (Cushing's Syndrome) by the Estimation of Urinary Androgens, *Quart J Med* 8: 273-249, 1939.

<sup>1264</sup>Anderson, A. F., Haja, A. M. and Patterson, J. Adrenal Carcinoma, Hormonal Diagnosis From Excretion of Pregnenolol, *J Pathol & Bact* 58: 341-349, 1945.

<sup>1265</sup>Hirschmann, H., and Hirschmann, F. R. Steroid Excretion in Case of Adrenocortical Carcinoma, *J Biol Chem* 157: 607-612, 1949.

<sup>1266</sup>Albright, F. Cushing Syndrome, *Harvey Lect* 38: 182-90, 1943.

<sup>1267</sup>Anderson, E. and Haymaker, W. Cushing Syndrome, *J Nerv & Ment Dis* 99: 11-20, 1944.

<sup>1268</sup>Horner, K. Ueber das Auftreten und Entstehen der Striae cutaneae, *dissem. Med. Welt* 29: 1071-1072, 1936.

## CHAPTER XIX

# DISORDERS OF THE ENDOCRINE GLANDS

## THE TESTICLES

The gonadatropic hormone of the anterior pituitary stimulates the Leydig cells in the connective tissue stroma of the testicle to produce the male sex hormone testosterone. It is excreted in the urine as androsterone which is a 17 ketosteroid. Both forms are often referred to as androgens. The international unit is the capon unit which is the biological equivalent of 100 micrograms of androsterone. Wolf<sup>1934</sup> enumerates as functions of testosterone the development and maintenance of the accessory sexual apparatus, the growth and distribution of hair, the maturation of the skeleton, the larynx and the muscles, the distribution of fat, the control of libido and potency, and the determination of the masculine psychological pattern. The excretion of androgen which is only 1 to 15 I U per day in childhood rises at puberty to 40 to 60 I U in the male and 25 to 40 I U in the female. The reverse relationship prevails with regard to estrogenic hormone output. Beyond the age of 60 the androgens decrease<sup>1940</sup> but do not completely disappear as is the case with estrogens in old women.<sup>1946</sup>

The androgens are chemically only slightly different from the estrogens, cholesterol and the bile acids (see also introduction to chapter on puberty).

Many facts demonstrating the influence of the testicle on the skin of animals are known.<sup>1938</sup> The best studied is the growth of the comb of the cock. Well known are the modifications of the plumage in male female and castrated chickens. In some species however e.g. the guinea fowl the plumage is not dependent on the gonads. The castrated male deer develops a peruke, a hairy growth instead of the antlers. In the reindeer which has antlers in both sexes castration is not followed by this malformation. In the Egyptian antelope *Portia pictus* the male is gray and the female brown. The hair of the castrated male takes on the same color as the female (Zawadowsky after Sand<sup>1941</sup>).

Comparable to the gonadal relations of the apocrine glands in man are the atrophy of the preputial glands in castrated mice<sup>1932, 1937</sup> and of the scent glands in the male goat.<sup>1941</sup> The improvement of the pelt in spayed animals<sup>1932, 1938</sup>

<sup>1930</sup>Flahler F. Sexualhormonbefunde im Harn von Männern verschiedenen Alters. *Zucker f. exper. Med.* 88 650-65 823

<sup>1932</sup>Sand H. Die Physiologie des Hodens. Hirsch. Handb. d. inneren Sekretion, vol. 2, Leipzig 1932. Curt habisch

<sup>1937</sup>Van H. E. Die Präputialdrüsen der Maus in ihrer Abhängigkeit vom Hormon des Hodens. *Stark f. Zellforsch.* mikr. Anat. 19 200-23 1931

<sup>1938</sup>B. erber W. Die Hautdrüsenorgane (Hauterische Drüsen, Inguinaldrüsen, Präputialdrüsen, Axillären, Handdrüsen, Kieferdrüsen der Laboratoriumsmaus) und die Fragen ihrer Abhängigkeit von den Geschlechtsdrüsen. *Stark f. Zellforsch.* mikr. Anat. 18 317-313 1 13

<sup>1941</sup>Chataignon. Action de la castration sur les glandes odorantes de la bœuf. *Compt. rend. Acad. de Med.* 1941 823 1971

<sup>1946</sup>Schmidt F. Fellveränderung nach Kastration. *Klin. Wochenschr.* 23, 1946

<sup>1946</sup>Polo von. Der Einfluss der Hypophysenhormone von nach Versuchs auf die Produktion der Wolle und die Entwicklung der Körperform des Schafes. *Tierärztl. Monatsschr.* vol. 8 83-79 1930

seems to be in contradiction with the favorable effect on the fur following the administration of testosterone or transplantation of testicular tissue in senile dogs.<sup>1267</sup> Castration and testosterone treatment demonstrated the gonadal dependence of the striking fur characteristics of the male baboon.<sup>1268</sup> The pig ment formation in man is also stimulated by testosterone (Milro after O Henslein 41)

The reduction of the readiness for anaphylaxis by removal of the testis and the restoration of a normal capacity for allergization by hormonal substitution has been demonstrated by Yun (after E. Urbach). The number of mitoses in the epidermis and hair follicles of the male white mouse decreases substantially after castration.<sup>1269</sup>

Much evidence has been accumulated suggesting a stimulating effect of androgens on number, size and function of the sebaceous glands, oil glands, and thickness of the epidermis<sup>1270, 1271</sup> and an increase of the production of prepuccial smegma.<sup>1272</sup> Acne hirsutism, obesity, husky voice and enlargement of the clitoris has been observed in women who have been treated with testosterone propionate because of menstrual disturbances.<sup>1273</sup> Folliculitis of the nose and of other parts of the skin and acne occur sometimes in men who receive androgenic therapy.

### Eunuchism and Eunuchoidism

Eunuchism is the syndrome resulting from loss of the testes while eunuchoidism characterizes the state of gonadal deficiency in the male.\*

**Early Castration.**—Loss of the testicles before puberty causes prolonged patency of the epiphyseal clefts with resulting excessive length of the extremities and fingers. The voice does not change, the muscles fail to gain the masculine strength and no libido develops.

**Dermadromes.**—Most striking is the failure to develop the sexual characteristics. The penis remains small and may be retracted into the scrotal skin which is thick and not unlike the labia majora. The body hair is scanty and the beard is absent with the exception of a little lanugo on the upper lip. In later age a scanty and bristly old women's beard appears on the chin and around the angles of the mouth. If there is a development of pubic hair it is of the female type. The hair line along the forehead does not develop, the temporo-frontal

\*The term eunuchism and eunuchoidism should be reserved for gonadal deficiency in the male.  
<sup>1267</sup>Zahler H. Rejuvenation of Senile Dogs by Means of Testicular Preparations and Their Effect on Testicles and Prostate, *Virchow Arch. Path. Anat.* 366: 85-107, 1926.

<sup>1268</sup>Lechman N. and Parker A. B. Secondary Sexual Characters I. Monkeys (Castration). *J. Endocrinol.* 1: 470-48, 1939.

<sup>1269</sup>Ortiz Plata, J. M. On the Effect of Castration on the Proliferative Activity of the Epidermis and of the Hair Follicles, *Rev. españ. biol.* 9: 43-46, 1933. *Ibid.* 38: 113.

<sup>1270</sup>Hooker C. W. and Pfeiffer C. A. Growth Effects of Sex Hormones Upon Bod. Growth, Skin, Hair and Sebaceous Glands in Rats, *Endocrinology* 52: 60-78, 1943.

<sup>1271</sup>Rony H. R., and Zakon, S. J. Effect of Androgen on the Sebaceous Glands of Human Skin, *Arch. Dermat. & Syph.* 68: 40-404, 1943.

<sup>1272</sup>Hamilton, J. B. Male Hormone Substances. Prime Factor. *J. Clin. Endocrinol.* 1: 570-593, 1941.

<sup>1273</sup>Greenhill, T. H. and Freed, J. O. Virilism in Women Caused by Androgenic Therapy for Menstrual Disturbances, *J. A. M. A.* 122: 1573-1574, 1939.

notch which is to a large extent characteristic of the male. It stays straight or is gently rounded (see puberty). The scalp hair seems to be vigorous. The same is sometimes true of the eyebrows and eyelashes. (H Fischer after Löwenthal<sup>1274,1275</sup>) Some authors however emphasize that the eunuchs fail to develop bushy eyebrows which are seen in many men after the fourth decade.<sup>1276</sup> It is known since antiquity (Aristotle) that eunuchs do not become bald headed like many other men. However precocious graying is mentioned.<sup>1277</sup>

**Late Castration**—If the loss of the testicles occurs after puberty the changes are less pronounced and even libido and potency may remain to some degree. The observations on such cases are plentiful. Hot flashes are felt by some castrates shortly after the loss of the testicles but they do not become as distressing a symptom as sometimes occurs in the female climacteric. There is a tendency towards loss of body hair<sup>1278</sup> which usually takes on a female distribution.<sup>1279</sup> A patient of Lasser<sup>1284</sup> who shaved four times weekly before the loss of his testicles had to shave only once a week afterwards. In some adult castrates the beard remained unaffected.<sup>1278,1279</sup>

The skin of the eunuchs is rather thin and remarkably pale with a slightly yellow hue. The pallor which is an outstanding characteristic of the eunuch's skin is caused by narrowing of the arterial bed and by a relative lack of melanin resulting from the failure of a colorless promelanin to mature to dark melanin. Probably because of this fact there is little or no tanning on exposure to ultra violet light.<sup>1280</sup> Similar phenomena are known in the female (see menstruation). Castrates who work outdoors like some members of the Skoptsy a religious sect in Russia and Rumania which practices castration for religious reasons do not acquire the typical farmer's skin.<sup>1276,1278,1281</sup>

The yellow component of the castrates' skin is caused by carotene which is present in excessive quantity.<sup>1282</sup> Pallor pigmentation and carotene content can be influenced by testosterone administration. The panniculus adiposus is often increased with concentration on the thighs the hips and the abdomen. Weight gains of twenty five pounds are common and the basal metabolism is usually lowered.<sup>279</sup> Some eunuchs however are lean. Gynecomastia is common<sup>1283</sup> but the breasts consist of fat only and not of glandular tissue.<sup>127</sup>

<sup>1274</sup>Löwenthal, K. Der Knochenbau des Mannes, Beitr. z. path. Anat. u. z. allg. Path. 36 426-439 1931

<sup>1275</sup>Schaefer O F. Die Behaarung d. Menschen, Leipzig, 1933. Curt Kabitzsch.

<sup>1276</sup>Tandler S. and Gross, J. Die Skopten. Einfluss der Kastration auf den Organismus, Arch. f. Entwicklungs- u. Org. 28, 2 232-253, 1910

<sup>1277</sup>Jarashon, H. Manual d. las enfermedades endocrinas y del metabolismo. Libreria Nacotta, Buenos Aires, 1930

<sup>1278</sup>Hackfeld A W. Ueber die Kastration bei 40 sexuell Abnormen, Monatsschr. f. Psychiat. Neurol. 87: 1-31 1932

<sup>1279</sup>McCullagh E P. and Renshaw J F. Effects of Castration in Adult Males, J.A.M.A. 193 1140-1143, 1934

<sup>1280</sup>Edwards, F A. Hanks J B. Duhey R A. and Hbert G. Osteogenic Vascular and Pigmentary Changes in Castrated Men, Endocrinology 23: 119-128, 1931

<sup>1281</sup>Koch, W. Die russisch-armenische Kastratenzeit; der Skopten Verfassung u. d. Kriegskonstruktionspat. 2 1-30 1931

<sup>1282</sup>Piquard, E. La castration chez l'homme. Recherches sur les adeptes d'une secte d'origine mystique, les Skoptsy Arch. scienc. d'anthrop. gén. 8 212-226 1913.

<sup>1283</sup>Lager, J. Die Folgen der Entmannung (an Hand der Kriegsverfahrenen dargestellt.) Leipzig Georg Thieme, 1934

The face often has a sleepy expression. This is caused by a small fat pad in the upper eyelids which narrows the space between the lids. Slight puffiness of the face is an early and common symptom after adult castration.<sup>1236</sup> The face often becomes finely wrinkled in a peculiar shriveled or papyraceous way which does not correspond to the normal facial folds.

Increase of the thickness of the nails in an adult castrate which could be reversed by testicular substance was seen by Lissac<sup>1234</sup> although nail changes were missed in the twelve cases of McCullagh and Renshaw.<sup>1235</sup>



Fig. 90 — Eunuchoid in young man aged 18 years. Beard, axillary chest, pubic hair absent. Frontotemporal hair line without masculine notch.

All or some of the features of eunuchism may be seen in the syndrome of eunuchoidism which is not rare as the experiences in the military induction centers have shown. Heredity is a factor in this constitutional endocrine anomaly.<sup>1236</sup>

The *male climacteric* is an objective reality<sup>1236</sup> and not mainly a matter of neurasthenia and hypochondry.<sup>1237</sup> However no definite dermatromes which

<sup>1234</sup>Lissac, H. Onychomaxia in an Eunuchoid. Remarkable improvement by implantation of Testicular Substance. Arch. Derm. & Syph. 10: 106-123, 1924.

<sup>1235</sup>Carmichael, M. T. and Kenyon, A. T. Eunuchoidism, Arch. Neurol. & Psych. 49: 717-742, 1925.

<sup>1236</sup>Heller, C. B. and Myers, O. B. The Male Climacteric. J. A. M. A. 125: 472, 1944.

<sup>1237</sup>Kluck, T. Das Problem des männlichen Klimaks, Wien. Klin. Wchnschr. 60: 1123-1129, 1926.

are linked to the physiological decline of the testicular function have become known. The keratoderma palmarum et plantarum climactericum described by Haxthausen in the female has also been reported in ageing men.<sup>1336</sup> In a recent analysis of 54 cases of the male climacteric,<sup>1337</sup> itching hot flashes and sweating occurred in about one third of the instances. Androgenic therapy seems to be promising.

### Common Baldness

Since the common type of baldness occurs almost exclusively in men it is natural to think of causes peculiar to the male sex. R. O. Stein<sup>1338</sup> who first described the calvities frontalis (see puberty) which is largely characteristic of the male hairline and is usually lacking in eunuchoids and women has suggested that the common baldness of males is a continuation of the physiological frontal baldness. Seborrhea and tension of the scalp with impaired circulation are contributing factors. Several authors<sup>1339,1340</sup> suggest that baldness of the common type is a generalized primate trait which occurs in a similar pattern in apes and monkeys. Heredity is a definite factor.<sup>1339,1341</sup> In 1932 Sabouraud<sup>1342</sup> quoting the famous observation of Aristotle that neither the child nor the woman nor the castrate become bald added that we know hardly more on the subject. The situation does not seem to have changed. However we have learned that administration of male hormone to eunuchoids and castrates can produce baldness of the common type. Premature alopecia of the male type has also been seen in virile women with arrhenoblastoma or suprarenal virilism. It ceases to progress when the abnormal masculinization ends.<sup>1344</sup>

Unfortunately endocrinology has not yet shown a practical way to prevent or cure baldness. Castration prevents baldness but this surgical approach has so far not been suggested in seriousness though it has been hinted.

### Gynecomastia

Gynecomastia may occur in an otherwise normal puberty. Ten cases were recorded per 100 000 personnel in the United States Navy.<sup>1345</sup> The type occurring in otherwise normal young men is more often unilateral than bilateral.<sup>1346</sup> It is also occasionally seen in the male climacteric.<sup>1347</sup> It is often pronounced in Fröhlich's syndrome and in eunuchoidism. In rare instances it is associated with a variety of neoplasms which have retained the endocrine functions of the

<sup>1336</sup> Haxthausen G. Palmar and Plantar Keratoderma, Schwed. med. Wchnschr. 73: 666-67 1940.

<sup>1337</sup> Wender A. A. Male Climacteric. 84 Cases. J. A. M. A. 227: 706-710, 1945.

<sup>1338</sup> Stein R. O. Ueber die Bedeutung des Haarwachstums und des Haarverlustes zum endokrinen System und über die Möglichkeit einer endokrinen Therapie der Glatze. Wien. Klin. Wchnschr. 49: 449-452, 1936.

<sup>1339</sup> Miller O. R. J. Human Hair and Primate Patternings, Smithsonian Misc. Collect. 95: 19, 1921.

<sup>1340</sup> Bat sur H. Ordinary Baldness. Arch. Dermat. & Syph. 43: 201-212, 1911.

<sup>1341</sup> Chohort D. I.heritance of Baldness. J. Hered. 7: 347, 1916.

<sup>1342</sup> Hammond J. R. Male Hormone: Insulation is Prolonged and Incident to Common Baldness, J. Intern. Dermat. 8: 472-474, 1943.

<sup>1343</sup> Weber O. V. Gynecomastia in the Male. M. B. J. 38: 375-379, 1915.

<sup>1344</sup> Mayfield J. G. Gynecomastia, Hygiea 21: 187-189, 1912.

<sup>1345</sup> Richardson, T. H. Gynecomastia, Lancet 1943, 1: 204-205.

soil from which they originated. Such tumors include<sup>1298-1300</sup> instances of adrenal cortical tumor<sup>124</sup> 1900 eosinophil adenoma of the anterior pituitary pinealeoma neoplasms of the midbrain or of the hypothalamus and thymic tumors. The best known endocrine neoplastic cause however are tumors of the testicle especially teratomas and the rare chorionepitheliomas with high estrogen production<sup>400</sup> 1900.



Fig. 191.

Fig. 192.

Fig. 193.

Figs. 1 191, 192, 193.—Pseudohermaphroditism. Female aged 10 years. Ovaries, infantile size, length of 10 cm. length, female distribution of pubic hair but visible phallus of 4 cm. scrotal pouch above of labia majora, male breasts, male body configuration, hairy voice, vigorous beard growth. Lives as girl. (Courtesy Wisconsin General Hospital.)

<sup>1298</sup>Weber, F. P. H. gynecomastia.—Endocrine Tumors, M. Press 212: 185-187, 1914.

<sup>1299</sup>Kries, H. Ueber Gynecomastie ein Beitrag zur Kenntnis der Beziehungen zwischen Hormondrüsen und Geschlechtscharakteren, Arch. Gynäk. 141: 303-337, 1920.

<sup>1300</sup>Geschickter, C. F. Suprarenal Tumors, Am. J. Cancer 23: 104-124, 1933.

<sup>1301</sup>Starckmann, A. R. Ein Fall von Chorionepitheliom im Hoden mit Gynecomastie, Frankfurt. Zeitschr. f. Path. 43: 40-57, 1933.

<sup>1302</sup>Jordan, O. H. W. Gynecomastie bei einem Kranken mit malignem Testikular-ova, Nederl. Tijdschr. Geneesk. 77: 39: 3-7533, 1933. Ed. 48: 150.

<sup>1303</sup>Lundin, B. Maligne Hodentumoren und Hypophysen-oder-Hypothalamus-Hormonale Herabsetzung Diagnostik aus Harn, Hydroxyketonwertigkeit und Tumorenwerte, Klin. Wochenschr. 11: 374-376, 1933.

<sup>1304</sup>Gordon, W. O. Pathology of 142 Cases of Primary Neoplasms in Man, J. Urol. 43: 723-732, 1940.

<sup>1305</sup>Levin, M. L. Gynecomastia, J. Clin. Endocrinol. 2: 311-314, 1941.

<sup>1306</sup>Boss, H. K. and Evans, N. Chorionepithelioma in Male and Gynecomastia, Am. J. Surg. 80: 121-123, 1942.



This symptom has furthermore been seen to follow prostatectomy and the administration of cholesterol<sup>1407</sup> adrenal cortical extract<sup>1408</sup> and desoxycorticosterone (Doca)<sup>1409</sup>. It is a frequent finding in cirrhosis of the liver (see chapter on diseases of the liver). Failure of the cirrhotic liver to destroy estrogens may be the cause of gynecomastia in severe hepatic disease<sup>410</sup> (Zondek B. after Edmondson).

Testosterone has been shown to cause complete regression or reduction of the hypertrophy of the male breast in 26 out of 28 cases.<sup>1411</sup> Surgery has been recommended<sup>1412</sup>



Fig. 194.—Same patient shown in Figs. 191-193. (Courtesy Warlock General Hospital.)

### Hermaphroditism

The presence of testicles does not necessarily produce male sexual characteristics. Female hair and other sex characteristics have been found together with microscopically verified testicles.<sup>413</sup> In a case of hermaphroditismus veru

<sup>1407</sup>Deas, O. W.    Ritibestrol—(Estrogen)—Induced Gynecomastia in Male. J.A.M.A. 115: 2283-2284, 1940.

<sup>1408</sup>Bromstein, T. F.    Gynecomastia. Endocrinology 24: 874-877, 1939.

<sup>1409</sup>Lawrence, R. D.    Gynecomastia Produced by Desoxycorticosterone Acetate (Adrenal Preparation). Bri. M. J. 2: 118, 1943.

<sup>410</sup>Giam, S. J. Edmondson, H. T. and Bell, R. V.    Sex Hormone Changes Associated With Liver Disease (Gynecomastia in Cirrhosis). Endocrinology 27: 749-753, 1940.

<sup>1411</sup>Hoffman, W. J.    Gynecomastia, Hormone Therapy. Am. J. Cancer 36: 247-251, 1939.

<sup>412</sup>Williams, A. T. and Schwartz, A.    Intersexuality. J.A.M.A. 117: 2218-2221, 1941.

lateralis<sup>1294</sup> with a testicle in the right side of the scrotum and an ovary and uterus in the left side of the scrotum breasts, pubic hair and other characteristics were of female character <sup>423</sup> They changed to the male after the removal of the ovary and uterus.

### Tumors of the Testicles

Except for the symptoms of precocious puberty and gynecomastia which may be caused by tumors of the interstitial tissue of the testicles no skin manifestations seem to be known in tumors of the testicles.

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<sup>1294</sup>Lattimer T. K. Kagle, E. T. and Yeaw B. H. True Hermaphroditism, J Urol. 50 481-490 1943.

## CHAPTER XX

# DISORDERS OF THE ENDOCRINE GLANDS

## THE OVARIES

Our knowledge of the influence of the ovaries on the skin in animals is much greater than that of the comparable facts in man. In the capon it is possible to produce a female plumage by injections of folliculines.<sup>44</sup> The feathers of an adult capon are so sensitive to injections of estrogens and placenta extracts that the failure to inject the hormones one day a week in a series of daily injections is recorded by a black bar in the breast feathers in their regeneration after being plucked.<sup>45</sup> This pigmentary reaction can be used as a pregnancy test<sup>46</sup> utilizing urine which can be read in 48 hours. In the oophorectomized Leghorn chicken the injection of small doses of theelin in olive oil causes a change in the regenerating feathers from male type back to female so that alternating bands of female and male color can be obtained.<sup>47</sup> While the time for the regrowth of the hair after shaving is the same in both sexes in immature rabbits it is shorter in the mature female longer in the mature female castrate and shorter again in males feminized by estronization.<sup>48</sup> Infiltration of the capon skin with estrogen locally inhibits the characteristic feather changes seen in castrates.<sup>49,50</sup> Continued subcutaneous injections of estradiol benzoate produces shagginess and marked loss of hair in the rat. The estrogen treated rat has a thinner dermis and epidermis and the sebaceous glands are reduced in size and number. All these changes can be prevented by administration of androgen.<sup>51</sup>

The implantation of ovaries into the kidneys of castrated male guinea pigs produces intense pigmentation of the nipples unless these are situated in albinotic skin.<sup>52</sup>

<sup>44</sup>Caridrol F. De l'action d'extrait de follicules sur le plumage du coq domestique. *Copey read Soc d'biol* 118 522-530, 1915

<sup>45</sup>J. H. 31. D. Armour F. E. and Gustavson, B. G. Plumage and Oviduct Response to Female Hormone in Fowls, *Endocrinology* 31 349-354 1930.

<sup>46</sup>Greenwood A. W. and Mlyth, J. B. B. Diagnosis of Equine Pregnancy. *Proc Roy Soc London B* 18 2 7-357 1934

<sup>47</sup>Mitchell J. B. J. Action of Theelin on the Domestic Fowl, *Proc Roy Soc Exptl Biol & Med* 30 500, 1933

<sup>48</sup>H. C. H. and Fraser C. N. Effect of Ovary and of Urinary Estrogens on Growth of Hair in Rabbit. *Anat Rec* 77 155-16 1910

<sup>49</sup>Quinn J. P. and Harrows, W. H. Effect of Female Sex Hormone on Plumage Color. *J Hered* 24 330-332, 1933

<sup>50</sup>Greenwood and Mitchell. Variation in Plumage Response of Brown Leghorn Capons to Female, *Proc. Roy Soc London B* 118 97 122, 1935.

<sup>51</sup>Freud, J. On the Biological Tests of the Female Sexual Hormone. Menformon. Influence on Feathers, *Proc Roy Soc Physiol* 67 371 1932

<sup>52</sup>Bleich, H. and Schraff A. Experimentelle Untersuchungen über den Einfluss des Ovarial-Hormones auf die Pigmentbildung. *Arch f Dermat Syph* 163 244-293 1913

### Ovarian Insufficiency

In *aplasia* of the ovaries the pubic and axillary hair is sparse or lacking. The rest of the hair has in some cases been seen to be underdeveloped.<sup>163-165</sup>

In B. Bloch's<sup>163</sup> case juvenile cataract and poikiloderma were present.

*Primary ovarian insufficiency* may lead to a habitus with overlong extremities and also to dwarfism.<sup>163,166</sup> The syndrome of primary ovarian insufficiency is characterized by excessive amounts of urinary follicle stimulating hormone and low levels of 17 ketosteroids. There is lack of breast and uterine development and other symptoms of infantilism. The axillary and pubic hair is scanty but not absent. Albright and his coworkers believe that the growth of the axillary and pubic hair in females is not stimulated by the ovary but by an adrenal cortical hormone (see chapter on Puberty). Melanoderma and mild depressive psychosis in ovarian deficiency have been described by S. Block<sup>167</sup> and later by Bonilla<sup>68</sup> and Marañon (after Bonilla<sup>69</sup>).

Naturally a great amount of information is available on the female *castrate*. The cutaneous symptoms after castration of the adult female are essentially those of the menopause. However it should be emphasized that castration of the woman does not always change her appearance.

*Secondary ovarian hypofunction* clinically characterized by amenorrhea or irregularity of the rhythm and amount of the menstrual flow usually does not cause dermadromes, though hypertrichosis is frequently encountered.<sup>169-71</sup> The hypertrichosis may disappear with the restoration of a normal ovarian function. It seems that hypertrichosis in ovarian hypofunction is due to the relative weakness of the prohibiting effect of the estrogen. Such an imbalance may be caused by ovarian deficiency as well as by adrenal cortical hyperfunction. The urinary excretion of 17 ketosteroids has in many instances of hypertrichosis been found above the normal level.<sup>72-74</sup> Application of estradiol sal<sup>75</sup> and intra dermal injections of progynon are able to make the local hair growth disappear<sup>164</sup> but the effect cannot be relied upon. The administration of stilbestrol in primary

<sup>163</sup>Dach, R. Poikiloderma tropicans mit Mangel der Ovarien. Urogenitropathie. J. v. Kalarak. Uebertragbarkeit d. Parasympathicus. Schweiz. med. Wchnschr. 58: 752-756, 1920.

<sup>164</sup>Ortel, J. Ueber den angeborenen Mangel beider Eierstöcke. Kastration und Depigmentierung. Frankfurt. Klin. Wchnschr. 29: 477-481, 1923.

<sup>165</sup>Goldschneider, J. Ein Fall von Aplasie ovariorum mit pluriendokriner Dysfunktion und mit durch Transplantation von Ovarien behobbarer Amenorrhoe. Arch. f. Gynäk. 152: 100, 1923.

<sup>166</sup>Tarney, H. F., Kenyon, A. T. and Koch, F. C. Ovarian Dwarfism. J. Clin. Endocrinol. 2: 137-143, 1912.

<sup>167</sup>Block, A. New syndrome. M. Rec. 90: 941, 1916.

<sup>168</sup>Bonilla, E. Insuffisance ovarienne, mélanodermie et troubles psychiques. Rev. franç. d'endocrinol. 3: 405-426, 1933.

<sup>169</sup>Selawsky, Th. Hypertrichose bei Frauen. Arch. f. Frauenk. 13: 153, 1927.

<sup>170</sup>Lauer, H. Fertilization and Demasculinization of 17 Year-Old Girl by Injection of Stilbestrol. Endocrinology 27: 243, 1940.

<sup>171</sup>Strassmann, E. O. Endocrine Treatment of Masculine Hair Growth Associated With Menstrual Disorders in Women. J. Internat. Coll. Surgeons 4: 127-142, 1941.

<sup>172</sup>Hambler, E. C., Cuyler, W. K. and Baptist, M. Urinary Excretion of 17 Ketosteroids in Ovarian Failure in Hysterectomy and Vaginitis Syndromes. J. Clin. Endocrinol. 2: 782-771, 1941.

<sup>173</sup>Ortel, J. Amenorrhoe and Pregnenolone Excretion in Hypertrichosis. Lancet 2: 446-447, 1940.

<sup>174</sup>Mislove-Fletcher, J. C. and Albright, A. Absorption of Sex Hormones by Skin. Case of Facial Hypertrichosis Improved by Intradermal Injections of Estrogen. Proc. med. 48: 669-670, 1940.

amenorrhea is often followed by hyperpigmentation of the linea alba and nipples.<sup>143</sup> This was not observed in the stilbestrol treatment of menopausal complaints.

### Ovarian Tumors

Cysts and teratomas rarely cause dermatomes except those connected with hypoovarianism. Granulosa cell tumors in children may cause precocious puberty<sup>144</sup> but there do not seem to be skin manifestations in adult patients.

—5—



Fig 193. Precocious puberty. Female, aged 6 years. Removal of ovarian tumor at age of 2 years. Premature development started. Cervix and rest of adult size. Bone age 12 1/2 years. (Courtesy Wisconsin General Hospital)

<sup>143</sup>Davis, M. E. Boynton, M. W. Ferguson, J. H. and Rothman, H. Studies on Pigmentation of Endocrine Origin. I. Endocrinology 8: 125, 1945.

<sup>144</sup>Meyer, H. Some Aspects of Ovarian Tumors and Their Relations to Sex Characteristics, Am. J. Obst. & Gynec. 22: 657-713, 1931.

*Dysgerminoma*<sup>1400</sup> or seminoma ovarii is rare. This type of neoplasm has been observed in pseudohermaphroditic individuals. The external genitalia are in female. These tumors which usually occur in the second and third decades do not masculinize the patient.<sup>1400</sup>

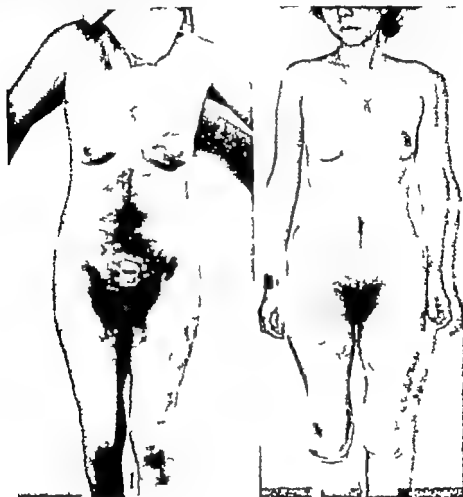


Fig. 96. Masculinizing ovarian tumor before and after operation. (From Blackman R. L. *Am. J. Obst. & Gynec.*)

*Arrhenoblastomas* cause defeminization and masculinization. Baldness of the masculine type may develop; characteristic deposits of fat may vanish; the breast, the other ovary, and the uterus may atrophy; and amenorrhea may ensue. There is enlargement of the clitoris, atrophy of the labia majora, and marked hirsutism of the male type with beard growth. The symptoms are reversible by successful operation. The tumors arise from the seminiferous tubules in the hilus ovarii or from a primitive ovotestis. The histologic picture

shows adenomatous structures resembling seminal tubules and/or epithelial cords. The endocrine testicular function accounts for the deep biological changes.<sup>142-144</sup>

In *Carcinoma*<sup>145</sup> *Luteoma*<sup>142-146</sup> *Sarcoma*<sup>146</sup> and *Hypernephroma*<sup>147</sup> masculinizing features have been described in rare instances. Kepler<sup>148</sup> observed



Fig. 197 — Female, aged 30 years. Facial hypertrichosis in ovarian tumor of unknown pathology.

Cushing's syndrome in a case of adrenal like tumor of the ovary. There was excessive excretion of 17 ketosteroids but a normal urinary output of estrogens. In rare instances<sup>149</sup> diffuse erythematous edema of the skin has been observed as a peculiar form of metastases from ovarian carcinoma (see chapter neoplasms).

<sup>142</sup>Milroy W. L. Arrhenoblastoma. *J. Obst. & Gynaec. Brit. Emp.* 49: 41-50, 1942.

<sup>143</sup>Andri, E. Geschlechtsanstimmung durch Ovarialtumor (Arrhenoblastoma). *Arch. f. Gynäk.* 119: 232-236, 1932.

<sup>144</sup>Milroy W. L. Ovarially enervated Arrhenoblastoma mit späterer Ach. anwachst. *Zbl. f. Gyn.* 87: 449-455, 1933.

<sup>145</sup>North, E. H. Arrhenoblastoma. *Am. J. Cancer* 22: 1-36, 1935.

<sup>146</sup>Leber H. Palmer A. and Morton, D. O. Arrhenoblastoma. Removal Followed by Fertilization and Pregnancy. (*Univ. L.* 765-781) 1942.

<sup>147</sup>Euse. Adrenal-ähnliche Gesichtshaarung. *Klin. Wochenschr.* 8: 1670-1671, 1929.

<sup>148</sup>Blackman H. L. Tumor With Masculinizing Syndrome. *Am. J. Obst. & Gynec.* 62: 1026-1041, 1942.

<sup>149</sup>Cosmides A. Dracopoulou S. Georgiou, M. and Dinkelsht, O. T. Luteinoma de l'ovaire: contribution au cas clinique à l'étude d'hyperandrogénisme ovarien. *Presse méd.* 80: 1261-1267, 1971.

<sup>150</sup>Milroy W. L. Masculinizing Luteoma. *Virchow Arch. f. path. Ana.* 209: 625-637, 1912.

<sup>151</sup>Goldberg. Mischgeschwulst des Ovarium (knorpelhaltige Sarkom) männliche Behaarung, Blinnveränderung und Adrenohypertrophie. *Zbl. G.* 22: 1163-1164, 1923.

<sup>152</sup>Trakaj, V. Hirnleukom d. Ovarialtumor. Heilung d. Entfernung der Gesch. mit Vrs. *Dtsch. Zbl. G.* 11: 1970 *Zbl. G.* 400.

<sup>153</sup>Clifford, E. Walcott J. and Smith, C. J. Diffuse Cutaneous Metastatic Lesions From an Ovarian Carcinoma. *Arch. Dermat. & Syph.* 110: 962-970, 1941.

Small blue *Angiomas Papillomas* and *Fibromas* in large numbers may occasionally accompany tumors of the female sexual organs<sup>144</sup> Such benign growths of the skin are seen in the menopause as well as in pregnancy and abdominal diseases

**Ovarian Relationship of Dermatoses**—In the light races women are supposed to be more often brunette than men<sup>145</sup> New investigations seem necessary The preponderance of the female sex in some dermatoses is well known Examples are hemangioma lupus erythematosus lupus vulgaris and some other types of skin tuberculosis scleroderma Raynaud's disease chloasma acrodermatitis atrophicans some circumscribed keratoses<sup>146</sup> urticaria pityriasis rosea eczema impetigo herpetiformis erythrocyanosis cruris erythema nodosum Paget's disease of the nipple tinea versicolor<sup>147 148</sup>

In order to accept the ovarian etiology in a given dermatosis the claimed relationship should be supported by menstrual or menopausal coincidence disappearance in pregnancy cure by hormonal therapy cure by castration after failure of other therapy and by other evidence of gonadal character The literature of the last fifty years abounds with such reports<sup>149-153</sup> However no dermatosis has been described which by its morphological picture alone would invariably permit the diagnosis of an ovarian dysfunction or disease

Cases of Purpura<sup>154-155</sup> psoriasis,<sup>156 157</sup> keratoderma palmare and plantare<sup>158-160</sup> erythema perstans<sup>161</sup> rosacea urticaria and angioneurotic edema

Men are more subject to the following dermatoses lichen sclerosus, herpes planus epidermophytosis inguinale, Kayser's keratoderma pigmentary sarcoma, cancer of the lower lip and mouth, and some others

<sup>144</sup>Tromsd, H. W. Haut bei sich angeregt u. gynäk. kranken Frauen, Arch f. Dermat. 87: 419 1903

<sup>145</sup>Havlicek, Ede. Haut und Weib, Würzburg, 1900, Curt Kabitzsch

<sup>146</sup>Korak, J. Beziehungen zwischen Haut und östlichem Genitale Biologie und Pathologie des Weibes, vol. 3 Berlin, 1937 Urban & Sch. warzburg

<sup>147</sup>Allen, E. V. The Relationship of Sex to Disease, Ann. I. Med. 7: 1000-1012, 1934

<sup>148</sup>Scharrer, O. Histopathologisches über die Ursache bei Frauen, Berlin, 1911 Urban & Schwarzenberg

<sup>149</sup>Rühl. Mesenterische Hämorrhoiden, Derm. Wochschr. 54: 241 1912.

<sup>150</sup>Wiener, E. Die Beziehungen der Genitalorgane zu Hautveränderungen, Halle 5 1924 Carl Marhold

<sup>151</sup>Castillo, C. A. Sobre purpura ovárica, Rev. med. e d. endocrinol. 21: 767-784 1932.

<sup>152</sup>Urbach, E. Endokrin bedingt jahreszeitlich auftretende Purpura, Zbl. 42: 64 1933-1935.

<sup>153</sup>Schneider, G. H. Leber konstit. heredit. menstruelle rheumatoide Purpura, Folia haemat. 22: 418-421 1929.

<sup>154</sup>Leit, E. Purpura bei Ovarialfunkt. lost. Monatsschr. f. Geburtsh. u. Gynäk. 81: 241-252 1939

<sup>155</sup>Loewell, O. Purpura Artthropathy in Women Whose Ovaries Have Been Removed Ophth. therapy Refractive eye pres. 48: 808-810 33

<sup>156</sup>Bot e-Miera, A. Su di un caso di cheratoderma simmetrica palmare plantare in donna amenorréica guarita con preparati opoterapici Riv. d'estet. ginec. prat. 12: 17 1930 Zbl. 54: 489

<sup>157</sup>Mitsui, T. and Shibata. Keratoderma tylosides palmaris progressiva Acta dermatol. japon. 11: 253-55 1929

<sup>158</sup>St. John, I. and Fajonaki, A. Erythema perstans und das endokrine System, Odessa med. J. 8: 649 1924 Zbl. 51: 303



(see menopause) <sup>1461 1466</sup> alopecia areata <sup>1466 1467</sup> eczema <sup>1467-67</sup> prurigo dermatitis herpetiformis <sup>1472</sup> parapsoriasis, <sup>673</sup> pruritus <sup>674</sup> and many other dermatoses have thus been linked to ovarian dysfunction. Bohnstedt<sup>1473</sup> found the urinary excretion of pituitary gonadotropic hormone increased in rosacea and dermatitis dysmenorrhea symmetrica. Chloasma in nonpregnant women and other pigmentations are in some cases of ovarian origin <sup>675</sup> They have occasionally been cured by local application of strong estrogen salve <sup>1477</sup>

<sup>1461</sup>Séjane de A.J., K. A. Urticaria pigmentosa, akutes Quincke'sches Oedem und Neurodermitis geheilt d. Thyroid- u. Ovarien-therapie, Actas dermo-sif. 23: 472-474 1930 Ebl. 86: 773

<sup>673</sup>Black, S. Durch endokrine Störungen bedingte Urticaria. Deutsche med. Wchschr. 54: 184-195 1929.

<sup>1466</sup>Elshové, V. Alopecia areata und Ovarialstörungen. Českosl. dermat., Samberger Festschr. pp. 330-334 1931 Ebl. 44: 423.

<sup>674</sup>Garnier H. Eczema Due to Estrogen-Lutein Disequilibrium: 3 Cases. Bull. Soc. franç. de dermat. et syph. 49: 319-327 1930

<sup>1467</sup>Desautels, A. À propos d la communication de St. Georges Garnier sur l'eczéma par l'déséquilibre hormonal folliculo-lutéinique. Bull. Soc. franç. de dermat. et syph. 48: 627-630 1929.

<sup>1472</sup>Burger St. Dermatologische Beziehungen einzelner Frauenkrankheiten endokrinen Ursprungs. Schweiz. med. Wchschr. 69: 36-37 1929

<sup>675</sup>Urbach, E. Endokrin bedingte Haut-, Schleimhaut- und Haarerkrankungen. Arch. f. Dermat. Syph. 181: 402-503 1930.

<sup>1465</sup>Esago, P. Eczema mit Ovarialstörungen. Gygyészet 66: 306, 1923 Ebl. 27: 783

<sup>676</sup>Kiecke, E. Dermatitis herpetiformis. Handb. d. H. u. Gk. 7: 3: 613, 1931

<sup>677</sup>Carlini, B. U caso di parapsoriasis (lichenoidi condilomatoso) guarito con la cura opoterapica. Giorn. Ital. di dermat. sif. 66: 1433-1437 1928.

<sup>1473</sup>Bohnstedt, R. von, and Liebhart, S. Hormonale Frauen Dermatosen. I. über einige präklimakterische und klimakterische Hautreaktionen. Dermat. Wchschr. 83: 1299-1303 1931

<sup>678</sup>Bohnstedt, R. St. U. Untersuchungen über Ausscheidung von Prolan A und Follükulin im Harn von Hautkranken. Klin. Wchschr. 83: 1675-1677 1934.

<sup>679</sup>Schölke, K. H. Chloasma symmetricum in nonpregnant women. Med. Welt 13: 1412-1414 1929

<sup>677</sup>Rocca, F. Estrogenic Substances in Treatment of Chloasma. J. Clin. Endocrinol. 3: 317-318 1942.

## CHAPTER XXI

### PUBERTY

Puberty is the transition from childhood to adult age seen mainly from the viewpoint of sexual maturing. In the female sexual maturing means the establishment of regular menstruation. In the male emission of semen must be considered the beginning of sexual maturity but this event is much less sharply accentuated and usually forgotten in adult life. Around the beginning of the production of mature gametes is grouped the development of the *secondary sex characters*. Furthermore puberty is a period of intensified organic growth and reorganization which affects almost every part of the body. Finally it is a period of psychic and intellectual ripening and adjustment. The onset of menstruation is but little speeded up by such factors as race and warmer climate probably more by urban life, better living conditions, and psychological factors.<sup>107</sup> In the United States the menarche starts between twelve and fifteen years, most frequently at 13.9 (Engelmann after Novak<sup>108</sup>) compared with 13.5 in the corresponding zone in Europe.

**Dermadromes of Puberty**—The establishment of the cycle follows within a year the growth of the pubic and axillary hair. The subcutaneous fat padding gradually smoothens and rounds the skeletal and muscular contours. Typical fat accumulations are found in girls on the cheeks, shoulders, breasts, buttocks, lower abdomen, mons veneris and thighs.<sup>109</sup> Girls develop less pigment than boys. Neurath<sup>11</sup> considers little bunches of veins in the skin of the thighs to be a female sex characteristic. In boys a palpable sometimes tender subareolar node of mammary gland tissue often appears at the onset of puberty and disappears at the end. Temporary gynecomastia in boys is seen occasionally.<sup>114</sup>

The *apocrine glands* start their secretion at puberty earlier in girls than in boys. These glands represent a type of skin gland which is in close relationship to the gonads. The apocrine glands are sweat glands which develop from the hair follicles and open into the hair follicles which the ordinary sweat glands, the so-called small or eccrine glands never do. They do not secrete sweat but give off a secretion consisting of particles of the secreting cell protoplasm. Thus their type of secretion places them between the sebaceous and the sweat glands. Many authors consider the apocrine glands to be a rudiment of the scent glands of many mammals. Such glands are known to have a close relationship to the sexual life. The peculiar odor of the human axilla which is different from the

<sup>107</sup>Novak E. Menstruation and Its Disorders, New York, 1931, H. Appleton & Co.

<sup>108</sup>Neurath R. Physiology and Pathology of Puberty. In von Pirro and Ackermann: The Diseases of Children, vol. I Philadelphia, 1933, J. B. Lippincott Co. pp. 307-336.

<sup>109</sup>June F. T. and Shafren, A. L. Mastitis, Mastopathy, Mastalgia, and Gynecomastia in Normal Adolescents. J. Pediatr. 1935, 11: 118-123, 1935.

odor of sweat may be due to the chemical characteristics of the apocrine glands which contain iron fat and cholesterol in remarkable amounts.<sup>140</sup>

In man the apocrine glands are most densely grouped in a heavy organlike layer in the center of the axillary fossa. Less concentrated groups occur in the pubic area particularly in the mons veneris and also around the anus in the areola mamillae (Montgomery's glands) and in the external ear ducts.<sup>141</sup> The thick layer of apocrine glands in the axilla is practically nonexistent in childhood. It is more pronounced in the female and much more developed in the Negro than in the white man.<sup>142</sup> It develops early in puberty. It is discernible several years before the onset of menstruation.<sup>143 144 145</sup> Some relationship to menstruation pregnancy and lactation has been claimed<sup>146</sup> but the matter is still controversial. Fox Fordyce disease is a chronic inflammatory condition of the apocrine glands (See Fox Fordyce disease). The axillary concentration of the apocrine glands atrophies slowly in the menopause.

The sweat glands especially those of the hands are often remarkably active during puberty.

The activity of the sebaceous glands is stimulated in puberty. This fact together with the keratosis of the follicular opening results in seborrhea and in the formation of comedones and acne. Comedones must be considered a physiological development of puberty since they can be found in almost every adolescent.

In childhood there are no differences in length abundance diameter and distribution of the hair. The sexual characteristics of the hair develop during puberty. At first there is no noticeable difference in the shape of the escutcheon of the two sexes.

After the seventeenth year the male pubic hair extends in a triangle along the midline toward the navel while the female escutcheon has a sharp horizontal upper border line. This however is not always the case. About one out of eight men has a female distribution of the hair often connected with subnormal beard growth and other feminine stigmata.<sup>147</sup> The lack of vigorous pubic hair growth is generally considered a stigma of infantilism. The lanugo in the male is coarser often pigmented especially on the chest the arms the legs on the perineum and around the anus. The hairs in the nostrils and ears tend to become coarser in later years. The hairiness in males can reach very similar varying degrees.

The pubic and facial hair in the female is probably stimulated by the adrenals rather than by the gonads since the axillary and pubic hair is not completely absent in the primary ovarian failure (X chromosomal dwarfism). It appears at puberty when the excretion of 17 ketosteroid rises probably due to adrenal cortical activity.

<sup>140</sup>Hieb, W. Anatomie der apokrinen Haut drüsen des Menschen mit besonderer Berücksichtigung des Achselhöhlenorgans. *Virchow Arch f path Anat* 287 277-286 1923.

<sup>141</sup>Stink, F. Normale Anatomie der Haut. Handb d H. Ok 1 1 1-269 1927.

<sup>142</sup>T. priner. Histologie des A. h. des Menschen und of Fox Fordyce. *Dermat. Wchnschr* 197 7 4 1923.

<sup>143</sup>Kayle, T. Histologie d. Haut. Berlin, 1923, Julius Springer.

<sup>144</sup>Klar, J. Das Achselorgan beim Menschen. *Wien klin Wchnschr* 88 127-131 1926.

<sup>145</sup>Blum, E. Über die verschiedenen Arten der männlichen Genitalhaare. *Klin. f. Konstitution* 18 164-176 1920.

The prepuberty male castrates develop slightly less pubic and axillary hair than normal females. Oophorectomized females do not lose their body hair however it falls out in Simmonds disease Addison's disease myxedema and very old age. In all these conditions the excretion of 17 ketosteroids is very low<sup>84</sup> The axillary hair also disappears in hepatic cirrhosis (see cirrhosis)



Fig. 195. — Male distribution, sternal patch of hair. N other endocrine abnormalities

Girls of course are supposed to have a smooth skin without noticeable hair except in the pubes and in the armpits. But quite often considerable hair growth along the legs, arms on the upper lip and even in the sternal region of the chest can be seen without any detectable endocrine abnormalities. This tendency is more pronounced in some pigmented races e.g. the mediterranean<sup>127</sup> <sup>128</sup> A peculiar accumulation of long pigmented hairs is not infrequently found around the female nipples although it is rarely seen in men.

During adolescence the *hairline* which is the border of the scalp hair acquires its characteristic configuration. The fairly straight frontotemporal hairline of children develops in boys a more or less marked triangular hairless notch which points in the direction of the vertex where the male baldness will develop later. According to R. O. Stein<sup>129</sup> who described this *calvities frontalis adolescentium* it is not observed in castrates nor in eunuchoids nor in women except in masculinizing conditions. This rule has not too many exceptions. The *calvities frontotemporalis* is seen in the vast majority of the men and in only less than 6 per cent of the women (Marañon after Musso Fournier<sup>130</sup>).

While the male hair in front of the ears unnoticeably merges into the beard sideburns are seen only in women who have other symptoms of hirsutism. Marañon (after Musso Fournier<sup>131</sup>) sees a sexual difference in the hairlines of the nape of the neck. In the female the borderline is distinct and shows two lateral prolongations and sometimes a medial one consisting of long hairs. In the

<sup>127</sup>Friedenthal H. Das Haarkleid des Menschen, Jena, 1904.

<sup>128</sup>Stein, R. O. *Eunuchoidismus*, Zbl. 18: 520 1926.

male the transition from the head hair into the lanugo of the nape of the neck is more gradual. This characteristic is not very pronounced. The male eyebrows are thicker, longer and less regularly implanted. They have a greater



Fig. 199 — Hypertrichosis of breast. The patient is obese, has strong facial hair growth and a decidedly masculine hairline. In detail, endocrine disturbance could be found. The 17-ketosteroid excretion was normal.

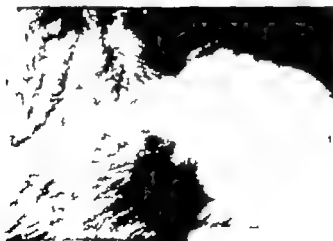


Fig. 200 — Female aged 30 years. Callosities corporalis in the same patient as shown in Fig. 199.

tendency to grow together on the glabella. The development of the eyebrows in the male parallels the general hairiness. In middle age some very long hairs appear in the eyebrows. In some men the eyebrows take on a bushy appearance

which is never observed in women. The *eyelashes* are stronger, longer and more curved in women than in men.

Shaving usually becomes necessary between the ages of sixteen and seven-teen. At first, the rate of beard growth is very slow, requiring shaving only once a month or less. Marañon (after Minello Fournier<sup>147</sup>) distinguishes a period of juvenile beard growth on the lateral upper lip, sygomatic, chin and sub-maxillary regions from the mature beard which forms by coalescence of the growth centers.

The color of the hair often deepens during puberty, particularly from sixteen to nineteen. This may be due to increased oiliness or to increased pigmentation (Brepohl after Jung<sup>148</sup>). The latter is true if there is a hereditary factor of pigmentation which had not yet become manifest. Blond Jewish children often darken considerably in this age.

Certain strands of elastic fibers in the skin of the face which have been described under the name of *elastica mimica* develop at puberty and degenerate



Fig. 20. Striae not related to pregnancy, sacrificed to loss of weight. Courtesy Division of Dermatology, Department of Medicine, University of Chicago.

slowly after the age of forty.<sup>149</sup> *Striae distensae* occur frequently in both sexes during adolescence. They are common in the skin of the lower back, across the thighs above the patellae and on the upper arms. They usually run transversely to the length of the body or of the limbs in symmetrical, rarely unilateral arrangement. In the lower back they are typically found in parallel lines below

<sup>147</sup>Jung, F. T. The Physiological Changes Incident to Puberty. Illinois M. J. 86: 477-484, 1941.

<sup>148</sup>Tschischke, K. H. Ueber die Altersveränderungen des Hautbindegewebes und über die angeborenen Elastica mimica bei verschiedenen Rassen. Derm. Ztschr. 88: 93-104, 1931.

the twelfth dorsal vertebra sometimes occupying almost the whole width of the back down to the center of the sacral area. Their<sup>1401</sup> appearance often coincides with growing pains in the limbs. The distribution of the striae in puberty suggests a mechanical factor. But it is likely that a toxin which weakens the elastic fibers plays a part. Some authors consider the appearance of striae in infectious diseases an ominous sign but there is little foundation for this belief. (See striae in chapter on pregnancy.)



FIG. 202 — Male aged 21 years. Striae of adolescence.

True *precocious puberty* is the phenomenon of early sexual maturity apparently not due to endocrine or cerebral disease but to unknown constitutional possibly hereditary factors. The constitutional type without endocrine tumor occurs in girls and is probably the most frequent variety of precocious sexual development.<sup>142</sup> The advanced development in these cases sometimes starts during intrauterine life. Menstruation without accompanying gross endocrine disease is known to occur several years before the normal time of onset.

All the sequences of puberty are hastened including the changes in skin and hair. The dermatologic aspect of early maturity is discussed in the chapter dealing with adrenal cortical tumors which are frequently responsible.

<sup>1401</sup>Peterson, O. *Verletzungen des Croissens bei den Jugendlichen*. Nouvelle Pratique Dermatologique, vol. VI, Paris, 1935, Masson & Cie, p. 85.

<sup>142</sup>Novak, E. The Constitutional Type of Female Precocious Puberty. *J. Amer. Med. Ass.* 104: 10-11, 1944.

Almost identical syndromes of precocious puberty can be caused by anterior pituitary hyperfunction by pinealomas<sup>442</sup> and other cerebral conditions of heterogeneous etiology.<sup>444</sup> The latter include tumors (glioma) of the corpora mammillaria hypothalamus<sup>446</sup> and other regions, brain abscesses, tuberculous sclerosis,<sup>446</sup> and encephalitis lethargica.<sup>447</sup> Precocity is also a part of Albright's syndrome (see there). It furthermore occurs in some conditions of the ovaries such as hyperovarium,<sup>448</sup> ovarian cysts,<sup>449</sup> arrhenoblastoma, teratoma,<sup>449</sup> and granulosa cell tumors. Precocious puberty is a characteristic of hyperorchism caused by neoplasms arising from the endocrinal (interstitial) part of the testis.

Delayed puberty is seen in connection with hypopituitarism, hypogonadism and hypothyroidism. In gonadal deficiency the thymus is usually persistent.<sup>450</sup>

### Skin Diseases of Puberty

*Acne vulgaris* is surely the most important and common dermatosis of the puberty age. Pollitzer<sup>440</sup> in 1914 gave its incidence in the United States as 7.5 per cent of all dermatoses, but it seems even more common today. There is hardly a boy or girl who is not at some time and in some degree afflicted with it. It is almost a physiological disease.

Follicular keratosis, comedo formation and seborrhea are the primary lesions of acne. Inflammation of acute or chronic character with or without abscesses and finally healing with a scar is the sequence of secondary symptoms. The face, back and the sternal region are most commonly involved. The microscopic examination of early lesions shows a follicular keratosis and epithelial atrophy accompanied by loss of the finer elastic fibrils near the epithelial wall.<sup>446</sup> This latter fact may account for the open pores.

*Gonads, Age, Sex*.—The most obvious relations exist with the gonads. Acne is extremely rare in early childhood, although it has been seen before the age of one year, especially in males.<sup>440-444</sup> From five to eleven years the incidence curve rises slowly, without severe cases. Then it soars distinctly, coinciding with the appearance of pubic and axillary hair, the development of the breasts

<sup>442</sup>King, J. F. Gieses, J. H. and Simon, H. Pubertas praecox. Pinealoma, J. Mt. Sinai Hosp. 6: 624, 1934.

<sup>443</sup>Carroll, P. La puberté précoce nelle cerebrogastri infantili, Rassegna di studi psichiat. 34: 833-860, 1933.

<sup>444</sup>Weinberger, L. M. and Grant, F. O. Precocious Puberty and Tumors of the Hypothalamus, Arch. I. Med. 67: 793, 1941.

<sup>445</sup>Curat, L. and Kluwe, P. Macroglanionomie précoce. Arrivées mongoloïdes. Adénomes adhésifs du visage. Rev. neurol. 1: 80-83, 1930.

<sup>446</sup>Ford, F. R. and Guild, H. Precocious Puberty Following Meno-Encephalomyelitis and Epidemic Encephalitis. Relation of Intracranial Tumors and Inflammatory Processes to the Syndrome of Macroglanionomie Praecox. Bull. Johns Hopkins Hosp. 90: 185-203, 1927.

<sup>447</sup>Zundel-Szodas, M. Fall von vorzeitiger Geschlechtsreife. Novy kair arch. 18: 810, 1933. Zbl. 31: 321.

<sup>448</sup>Sergius, H. Pubertas praecox als Folge chorioepitheliomatöser Wucherungen, Arch. f. Gynäk. 189: 49-53, 4: 832.

<sup>449</sup>Pollitzer, R. Acne Vulgaris, J. Cutan. Dis. 33: 315, 914.

<sup>450</sup>Lynch, F. W. Acne Vulgaris. Histologic Changes in Early Lesions, Arch. Dermat. & Syph. 63: 863, 1940.

<sup>451</sup>Querry, J. J. Infantile Acne Vulgaris, J. Pediat. 20: 365-367, 1932.

<sup>452</sup>Gray, A. M. H. Acne in Child Aged 2 Years. Proc. Roy. Soc. Med. 27: 392, 934.

<sup>453</sup>Atkes, R. Acne in Infants. Brit. J. Derm. 64: 373-375, 1943.



and the onset of the menses.<sup>1505</sup> Girls develop acne earlier in life. At the age of seventeen almost every boy or girl has some though often inconspicuous blackheads or pimples. The severe cases are seen in girls from fourteen to sixteen in boys between sixteen and nineteen.<sup>1506</sup> Boys have a little higher morbidity and show severe cases more often. This has been shown in investigations of many thousands of adolescents in various countries.<sup>1507-1507</sup>

Some statistics give a lower incidence but it seems that they only take into account the more severely inflammatory cases. After the age of twenty acne becomes less and less frequent but there is no sharp upper age limit. Even in the fourth decade acne is not uncommon in men and exacerbations in women at the onset of and even after the menopause occur. There does not seem to be acne vulgaris in the aged.

Next to the coincidence of acne with the onset of puberty the time relationship to menstruation suggests a gonadal factor. It is common knowledge and it has often been confirmed by medical observation that acne exacerbates before, during or after the menses, the individual case usually remaining constant to type with regard to the time relation of the exacerbation.<sup>1508</sup> The intermenstrual remission is often complete. However similar menstrual flare-ups can be seen in lupus erythematosus, psoriasis, rosacea, eczema<sup>1509-1510</sup> and other chronic dermatoses. Therefore the menstrual exacerbation itself is a weak argument for the gonadal cause, more so since it occurs in only a certain percentage which varies from about 30 to 75 per cent in several observed series of girls. Menstrual disorders and hypogonadism are no more frequent in girls with acne than in those without acne.<sup>1511-1514</sup>

A great deal of work with modern methods has been done in order to find better proof of an imbalance of hormones in juvenile acne than is furnished by statistical and clinical methods. This work showed that in patients with acne the output of estrogen in the urine is below the normal level. Rosenthal and Kurzrok<sup>1515</sup> and later Rosenthal and Neustaedter<sup>1516</sup> were unable to find any estrin in twenty-seven out of thirty-four young women with acne. These low urinary estrogen contents in patients with acne were confirmed by a number of authors.

In men with acne the excretion of estrogen was also found to be well below normal. On the other hand the output of androgen in men was found to be higher in acne patients while it was found in normal level in women. Only Cornbleet and Barnes<sup>1517</sup> found the daily urinary androgen output in male and female

<sup>1505</sup>Rösch, B. *So Pathogenese der Acne vulgaris*, *Exl* 46: 819.

<sup>1506</sup>Hirrichsen, J. and Ivy, A. C. Incidence in Chicago Region of Acne Vulgaris. *Arch. Derm. & Syph.* 37: 975-993, 1939.

<sup>1507</sup>Sch. Artzman, J. Abnormalities (Adolescence) *J. Pediatr.* 21: 93-102, 1912.

<sup>1508</sup>Craback, E. and Schiller, W. Der heutige Stand des Akneproblems. *Akne sexualis*, *Med. Klin.* 33: 1-61, 1937.

<sup>1509</sup>Cohen, E. L. Incidence of Chronic Acne in Men. *Lancet* 2: 109, 1912.

<sup>1510</sup>Jach. *Ueber die Beziehungen der Acne zu Allgemeinerkrankungen*, *Diss. Bonn*, 1907.

<sup>1511</sup>Cunningham, B. E. and Lane, C. J. Acne. *Revised Cases, California & West. Med.* 33: 25, 1931.

<sup>1512</sup>Rosenhal, T. and Kurzrok, R. Excretion of Estrin in Acne. *Proc. Soc. Exper. Biol. & Med.* 29: 1150-1151, 1933.

<sup>1513</sup>Rosenhal, T. and Neustaedter, T. Estrogenic Substance in the Blood of Patient With Acne. *Arch. Derm. & Syph.* 32: 560-563, 1938.

<sup>1514</sup>Cornbleet, T. and Barnes, B. The Hormones and Acne Vulgaris. *Arch. Derm. & Syph.* 40: 219-233, 1939.

patients with acne a low normal. Wile<sup>125</sup> and his collaborators impressed by the relatively high and unchanging androgen findings believe that the ratio between urinary androgen and estrogen is of great significance. They found its value in acne much higher about double of the normal figures. These observations have essentially been confirmed.<sup>126, 127</sup>

The excretion of sex hormones in the pre-acne age of less than eight is very small and the same for both hormones in both sexes. From eight to eleven both steroid sex hormones rise the androgen quicker in the male the estrogen quicker in the female. When adulthood is achieved the normal characteristic ratio of the excreted sex hormones is established.<sup>128</sup> Acne is characteristic for the years of transition when the ratio is changing just as it is characteristic for the catamenia. At this point of the menstrual cycle the urinary output of estrogens has reached its lowest level.<sup>129-130</sup> The androgens excreted by the woman do not fluctuate with the cycle so that a relative preponderance of androgens exists at and around menstrual time when acne is well known to exacerbate. There is much evidence that male eunuchoids do not have spontaneous seborrhea and acne<sup>131</sup> but may acquire it during treatment with androgenic preparations just as women and also men often do under treatment with testosterone propionate.<sup>132</sup> It is noteworthy that acne produced in eunuchoids by injection of testosterone propionate disappeared on withdrawal and reappeared on resumption of the injections.<sup>133</sup> Boys generally have an increasing incidence of acne from seventeen to twenty-one years and their cases are often more severe with a greater tendency to pyogenic infection and involvement of the trunk.<sup>134</sup> It is a general impression that virile boys are more likely to show acne than those of a more feminine type<sup>135</sup> and also that girls with severe acne are of less marked femininity. The occurrence of acne in masculinizing tumors of the adrenals the pituitary and the ovaries has often been observed. Zimmer<sup>136</sup> found gynecomastia more often together with acne than with normal skin but his series is small.

Long before it was possible to prove any changes in the level of sex hormones the attempt had been made to cure acne with organ extracts which in the light of our present knowledge probably had very little potency. Later a great number of investigations were made with preparations of undoubted potency. Anterior pituitary like gonadotropic hormone prepared from urine of pregnant women has been tried by scores of authors. While most of them found little or no

<sup>125</sup>Wile U. I., Shaw J. S. and Deadbury J. T.: Sex Hormones in Acne Arch. Dermat. & Syph. 59: 300-316, 1939.

<sup>126</sup>Lawrence C. H. and Wertheimer, W. T.: Endocrine Dyscrasia of Acne in Women, Endocrinology 27: 733-754, 1940.

<sup>127</sup>Lawrence C. H. and Wertheimer, W. T.: Acne in Females, Internat. Clin. 1: 186-205, 1943.

<sup>128</sup>Callaghan, J. T., Tresser L. E. and Aub, J.: Sex Hormones in Urine and Acne Endocrinology 23: 331, 1941.

<sup>129</sup>Smith, O. V. and Smith, M. W.: Urinary Excretion of Estrogens and Gonadotropic Hormones During Menstrual Cycle: Period of Conception and Early Pregnancy. New England J. Med. 215: 994, 1936.

<sup>130</sup>Dingemans E. and Laquer E.: Nederl. J. der. geneesk. 55: 3297, 1940.

<sup>131</sup>Grisel, H., Kaimowitz J., Gairola J. A. and Walter E. I.: Biologic Effects of Androgens (Testosterone Propionate) in Women, J. A. M. A. 116: 1529-1544, 1940.

<sup>132</sup>Hamilton, J. B.: Treatment of Sexual Underdevelopment With synthetic Male Hormone. A. M. J. Endocrinology 31: 649-654, 1937.

<sup>133</sup>Zimmer E.: Gynecomastia and Acne vulgaris, Dis. Erimera, 533.

value some claimed benefit.<sup>120</sup> Just as variable were the results with estrogens but it seems that good results outweigh the poor results though not very impressively. B. Zondek<sup>121</sup> showed that follicular hormones can produce estrus



FIG. 203. (left) Familial tendency, acne. F. her and son. (Right) mother and daughter.

phenomena if applied percutaneously. This has since been shown in many experiments. The practical application of this observation in the treatment of acne by ointments containing estrogens and androgens has mostly been disappointing.

<sup>120</sup>Lawrence, C. H. The Anterior Pituitary Hormone. A Clinical Study of Its Effects in Acne Vulgaris. *J. A. M. A.* 196, 943-957, 1939.

<sup>121</sup>Zondek, B. Local Treatment of Acne With Estrogen, *Schwela and Weinacker* 65, 1164-1169, 1935.

Luteal hormones have been recommended but have had little trial compared with estrogens. The alternating use of large doses of estrogens during the first ten days following the menses and luteal hormone on five consecutive days during the third week of the cycle was followed by lasting improvement in five girls after three months of treatment (Urbach and Schiller<sup>1467</sup>). Considering the fluctuating course of acne a sceptical attitude toward all reports of small numbers of cases is justified. Androgens have been tried in the treatment of acne in spite of the many experiences with their acneogenic effects. The reports are overwhelmingly discouraging. In several experimental series<sup>1468</sup> controls received injections of bland sesame oil. The effects were about just as good as with androgen in sesame oil—and both were not too poor. In summarizing the gonadal relationship of acne one is permitted to say that the age incidence, menstrual accentuation, occurrence in masculinizing tumors, nonoccurrence in male eunuchoids, urinary and blood content of sex hormones and the production of acne with androgen injections proves its existence. However the degree of our knowledge of the mechanisms involved has not yet yielded a reliable method of hormonal therapy. This opinion is reflected in a symposium on acne of leading American dermatologists. Not one out of five dermatologists used hormonal therapy to a larger extent than as an adjuvant.<sup>1467</sup>

*Hypertrichosis* in girls with or without other signs of endocrine disturbance usually causes a great deal of anxiety. The patients or more often the parents soon become worried about the possibility of serious pituitary or adrenal disease. After investigation this question is, fortunately, most often answered in the negative. But then the cosmetic problem remains. It is beyond the scope of this book to deal with the treatment of *hypertrichosis*. But it may be mentioned that endocrine therapy so far has only been successful if other endocrine symptoms, especially amenorrhea, were present.

The outbreak at puberty of *chronic dermatoses* like psoriasis, lupus erythematosus and epidermolysis bullosa has been observed sufficiently often to make coincidence unlikely.<sup>1469</sup> In Recklinghausen's neurofibromatosis the number of tumors existing from early childhood may suddenly increase so that the fully developed syndrome results. Onset of lipoma formation in puberty has become known in Dercum's disease. It seems correct that in adolescence the tendency to keloid formation is more marked than before. A keratosis involving the volar surfaces of the fingers of Japanese girls and mostly starting after the first menstruation has been described by Dohi and Miyake under the name of keratoderma tyloides palmaris progressiva. Takenaka<sup>1470</sup> reported 217 cases seen in ten years and Kawabe<sup>1471</sup> 50 cases.<sup>1472</sup> Dysmenorrhea and increased basal metabolism have frequently been observed. It seems that besides gonadal factors

- <sup>1467</sup>Mettich, M. Free Deal of Acne Vulgaris With Testosterone Propionate. *Endocrinology* 23: 603 1937.  
<sup>1468</sup>Symposium on Practical Management of Acne Vulgaris, *J. Invest. Dermat.* 3: 43-157 1946.  
<sup>1469</sup>Takenaka, S. Keratoderma tyloides palmaris progressiva. *Hitsu-to-Hitsuyo* 8: 292 1937. Ed. 87: 605.  
<sup>1470</sup>Kawabe, M. Die sogenannte Keratoderma tyloides palmaris progressiva. *Jap. J. Dermat. & Urol.* 21: 21 1932.  
<sup>1471</sup>Kitamura, S. Keratoderma tyloides palmaris progressiva (Dohi and Miyake). *Jap. J. Dermat. & Urol.* 23: 974-1 1929. Ed. 88: 165.

occupational causes play a part. The condition has rarely been seen in boys. The *favorable* influence of puberty is noticeable in certain dermatoses. This is true of urticaria pigmentosa and of infantile eczema. Only a small percentage of cases of infantile eczema are carried over into adult age in the form known as atopic dermatitis. Such a stubborn and resistant disease as tinea of the scalp particularly microsporia has a marked tendency to heal spontaneously at puberty although there are exceptions to this rule. The fact that tinea of the scalp usually heals at puberty may be due to the higher acidity during puberty. The pH of the infantile skin drops from 6.2 — 6.4 to 4.5 — 5.6<sup>101</sup>.

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<sup>101</sup> Bancroft, J. R. Hormones and Skin, California & West. Med. 61: 80-83, 1944.

## CHAPTER XXII

# MENSTRUATION

### The Menstrual Cycle<sup>138 139 140</sup>

The anterior pituitary by means of prolactin A a protein like hormone activates the ovary. The follicle-stimulating fraction of the prepituitary hormone causes the maturing of the graafian follicle during the first half of the menstrual cycle the luteinizing fraction prolactin B after the ovulation on the fourteenth day makes the corpus luteum grow in the empty follicle.

During the entire cycle the follicle secretes the steroid estrogens. The estrogen blood level reaches its peak immediately before the onset of the menses and drops to its lowest point during menstruation. There is another peak at the time of ovulation at midterm. The estrogens cause the proliferative changes in the uterine mucosa during the first two thirds of the cycle. The corpus luteum produces another steroid hormone progesterone which reaches its high in the circulation during the last third of the intermenstruum. It causes the premenstrual secretory changes of the uterine mucosa which are preparatory for the embedding of the ovum. If there is no fertilized ovum forthcoming the uterine mucosa breaks up and menstruation results. The corpus luteum wanes.

More than fifty years ago when menstruation was still believed to be a reflex von Ott<sup>141</sup> the first to speak of a menstrual cycle traced over a full month the pulse temperature blood pressure caloric loss muscular power capacity of the lungs and other physiological functions. He found that all these manifestations of vitality increased slowly in intensity during the whole intermenstruum to reach a maximum immediately before the onset of the menstrual flow. Then a steep decline during menstruation brings the levels back to the starting point. Since these studies many investigations have been made along the same lines. They mostly revealed parallel cyclic changes of vitality and reactivity. Many of the cyclic phenomena can be linked with cutaneous changes.

**Blood**—The number of erythrocytes decreases slightly during the intermenstrual period. During menstruation it first rises then falls and rises again after menstruation (Pöhl after Novak<sup>142</sup>). The hemoglobin fluctuation is slight. There is a moderate leukocytosis during the first day of menstruation.

The *thrombocytes* reach a maximum at the time of ovulation and a minimum during menstruation. Catel and Schotola<sup>143</sup> traced the decrease of the thrombocytes to the influence of the corpus luteum hormone and suggested the use of the reaction of the thrombocytes as a test for the potency of corpus luteum

<sup>138</sup>Frank, R. T. *Puberty, Menstruation, Pregnancy*, Baill. Tiney, New York Acad. Med. 16: 83-97, 1940.

<sup>139</sup>Van O. D. *Des lois de la périodicité de la fonction physiologique dans l'organisme féminin*, N. Arch. d'obst. et de gynéc. 5: 803-806, 1890.

<sup>140</sup>Catel, W. and Schotola, H. *Thrombocytes, Menstruation and Corpus-luteum-Hormone*, Med. Klin. 34: 973-976, 1940.

preparations. The tourniquet test is often positive before<sup>128</sup> and during menstruation<sup>128, 127, 129</sup>. The prothrombin level is probably lowered and the coagulation time lengthened shortly before the onset of menstruation. With menstruation rise of the prothrombin and return of the coagulation time to normal or even higher than normal takes place.

The blood sugar shows a premenstrual rise<sup>130</sup>. The carbohydrate tolerance is lowered in menstruating diabetic women and acidosis and coma may be precipitated. The more frequent occurrence of acidosis in women below forty five years of age than in males of this age may be linked to the influence of the menstrual hyperglycemia<sup>131, 132</sup>.

High blood cholesterol has in some cases been seen to return to normal during menstruation<sup>133</sup>. It seems that the blood cholesterol falls during or near menstruation and is followed by a rise above normal level<sup>134, 135</sup>.

There is a tendency to premenstrual water retention. One third of forty two women showed weight increase before and during the catamenia. In some cases edema is noticeable<sup>136, 137</sup> especially about the lower legs and ankles. The urticarial (lymphagogue) reaction to intracutaneous injections of minimal doses of morphine is stronger in the premenstrual period while the vasoconstrictive action of adrenalin is weaker at the same time<sup>138</sup>.

The general hydration is probably accompanied by increased succulence of the skin which explains the menstrually increased firmness of the hair implantation in the skin<sup>139</sup>. On the last premenstrual day it takes more than double the weight necessary to pull a hair out than at the end of the period.

<sup>128</sup>Nickel, L. Kann das End thelymenstron als Test für Diagnose und Therapie variabler Funktionsstörungen angesehen werden? Deutsche med. Wchnschr. 87: 1108-1109, 1931.

<sup>129</sup>Dryden, T. A. H. Einblutungsstörungen und Prämenstruum. München. med. Wchnschr. 28: 918, 1910.

<sup>130</sup>Adams, W. Der Prothrombospiegel im Zyklus der geschlechtlichen Frau. Zbl. f. Gynäk. 66: 1057-1061, 1912.

<sup>131</sup>Hirshdörfer, R. Prothrombin Level and Coagulation Time of Sexually Mature Women. Skand. J. d. gen. Spec. Med. 113: 27-31, 1913.

<sup>132</sup>Radel, J. Die Capillarreaktionen und ihre Beziehungen zur Menstruation bei der Frau. Klin. Wchnschr. 28: 266-26, 1911.

<sup>133</sup>Newton, H. C. and Herrington, F. Sugar Metabolism and Insulin Therapy in Acute Insulitis. Brit. J. Diab. 31: 477-483, 1932; 32: 123-129, 1933.

<sup>134</sup>Curry, H. J. The influence of Menstruation on Carbohydrate Tolerance. Canad. J. A. J. 47: 51, 1917.

<sup>135</sup>Kahler, H. Einfluss der Menstruation auf den Blutzuckergehalt. Wchnschr. 27: 917, 1911.

<sup>136</sup>Frankel, E. Cholesterin und Xanthine. Dermat. Ztschr. 21: 137, 1914.

<sup>137</sup>Osby, N. and Højden, R. E. Study of the Metabolism of Women. Lipid Content of Blood and Menstrual Cycle. J. Biol. Chem. 22: 261, 1927.

<sup>138</sup>Wieria, D. and Warrington, J. V. Tissue Resistance and Clinical Medicine. Boston, 1911. Little, Brown & Co.

<sup>139</sup>Osby, J. H. Menstrual Edema. Preliminary Report. J. A. M. A. 182: 271, 1921.

<sup>140</sup>A. Kline, A. J. and Ivy, A. C. Menstrual Edema. Controlled by Estrogens but not by Thiochloral Thiochloral. J. A. M. A. 186: 518-517, 1926.

<sup>141</sup>Mohr, and Gruber, L. Mit der Menstruation zusammenhängendes Ödem. skizziert. Ges. Klin. Wchnschr. 33: 269-273, 1917.

<sup>142</sup>Kröblich, A. and Linder, A. Schwankungen der Hautsensibilität der Haut bei Frauen im Abhängigkeit vom ovariell-menstruellen Zyklus. Fortschr. med. Wiss. 2: 22-31, 1912. Zbl. 45: 1.

<sup>143</sup>Reich, H. Menstruation und Haarwurzelbildung. Ind. Klin. 28: 1151-1153, 1934.

In the intermenstruum the resistance against pull rises to a medium figure. Newer investigations have in part failed to confirm these claims.<sup>120</sup>

Menstrual swelling of the liver was already observed by Chvostek.<sup>120</sup> Menstrual icterus has been the subject of several investigations.<sup>121</sup>

Von Leaczynski<sup>122</sup> found that in eighty seven out of one hundred menstruating women whom he tested with intracutaneous injections of 0.02 per cent trypan blue the disappearance of the deposit was faster than normal. This test seems to demonstrate an increased activity of the reticulo-endothelial system.

The sensitivity of the skin to ultraviolet light in the premenstrual phase is often higher than normal. The return to normal sensitivity to light occurs during menstruation beginning on the first day.<sup>123-125</sup> This may be correlated with the simultaneous fluctuations of the blood calcium potassium and iron<sup>126</sup> and especially of the estrogens. In this connection the observations of Hamilton<sup>127</sup> concerning the significance of the sex hormones in the tanning of the skin of women may be mentioned. In women who were either in the spontaneous menopause or castrated marked tanning occurred only after injection of estrone or testosterone propionate. Then the pigmentation appeared in areas which as long as two months previously had been exposed to light while areas protected by the shoulder straps and the bathing suit did not tan. Thus the steroid sex hormones acted like a photographic developer.

Spontaneous allergic reactions like asthma<sup>128</sup> as well as those elicited by tests are often stronger immediately before or during the catamenia. The sites of old positive intradermal reactions may flare up again during menstruation.<sup>129</sup> Patch tests are sometimes negative when done in the intermenstruum and positive when repeated during menstruation (Tzanck and Sidi after Urbach<sup>130</sup>). Urbach<sup>131</sup> advises not to increase the dose for pollen desensitization during the menses because of the possibility of acute reactions. The Dick test for scarlet fever is sometimes temporarily falsely positive during menstruation. On the other hand a negative Dick test during menstruation is to be considered highly reliable. Some observers<sup>132</sup> found the highest reactivity to various allergens on the last

<sup>120</sup>Waisaker W. L. Hair Root Strength and Menstrual Cycle, *J. Invest. Dermat.* 6: 306-307 1945

<sup>121</sup>Ortsock Die menstruelle Leberhyperämie, *Wien. klin. Wchnsch.* 8: 293-297 1908

<sup>122</sup>Leaczynski Menstruelle Gelbsucht, *Berl. klin. Wchnsch.* 8: 518-519, 1873.

<sup>123</sup>Leaczynski, K. von Ueber das Einflüsse der weiblichen Geschlechtsorgane auf das reticulo-endotheliale System der Haut, *Dermat. Wchnsch.* 181: 1108-1117 1925.

<sup>124</sup>Ortsock, H. and Vassil W. Ultraviolettlichtempfindlichkeit und menstruelles Cyclus, *Strahlentherapie* 68: 287-293 1933

<sup>125</sup>Dieterich, H. Das Lichtrythmus unter dem Einflusse von Menstruationszyklen und Schwangerschaft, *Strahlentherapie* 27: 847-850 1937

<sup>126</sup>Kühner F. Die Lichtempfindlichkeit der menschlichen Haut, ihre Bestimmung und Bedeutung für die kühnbiologische Konstitutionsforschung, *Strahlentherapie* 61: 1-82, 1912

<sup>127</sup>Freund, L. Menstruelle Störungen der Strahlenempfindlichkeit der Haut, *Wien. klin. Wchnsch.* 68: 83-85 1923

<sup>128</sup>Handlman, J. D. Fluorescence of Sex Hormones in Tanning of the Skin of Women, *Proc. Soc. Exper. Biol. & Med.* 44: 803-803, 1939

<sup>129</sup>Tilma R. Asthmaepisoden, *Mitt. KHM* 36: 569-571 1934

<sup>130</sup>Gans, O. Ueber spezifische Reaktionen der menschlichen Haut, *Dermat. Wchnsch.* 73: 841-845, 1927

<sup>131</sup>Harlow-Fraser, O. O. and Raymond, R. Skin Reactivity During Menstrual Cycle, *J. Clin. Endocrinol.* 2: 16 1932, 943



day of menstruation the next strongest in the midperiod and the lowest on the premenstrual day. Thus the greatest reactivity of the skin would coincide with the period of estrogenic deprivation. The sensitivity to tuberculin has been found greatly reduced during menstruation.<sup>103</sup>

There seems to be little or no influence of menstruation on the results of serologic tests for syphilis.<sup>104</sup>

**Menotoxin**—Popular belief has always held that a menstruating woman exerts a poisonous influence on her environment. Dough kneaded by a menstruating woman would fail to rise and fruit canned in this condition would not keep. In 1878 the British Medical Journal discussed the question whether the

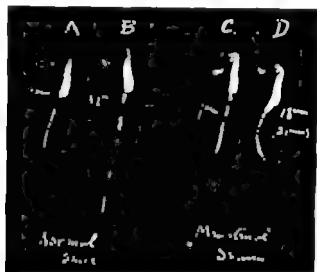


Fig. 301.—Toxic influence of menstrual serum on the growth of seedlings of *Lepidum albe*. A and C length of roots at the start. B root after 24 hours in 0.1% solution. D after 24 hours in 1% menstrual serum in 0.1% solution. The root has increased only 4 mm. instead of 18 mm. Normal serum inhibits the growth also but much less. (From Mackay, D. J. *J. Pharmacol. & Exper. Therap.*)

general belief was true that if a woman cured hams while menstruating the hams would spoil. Similar beliefs are found in almost all countries.<sup>105</sup> The question whether cut flowers wither quicker if handled by a menstruating woman was first studied seriously by Schick<sup>106</sup> who from his experiments believed that the blood and sweat of menstruating women exert a poisonous influence on cut flowers and yeast. He found a marked difference in the life time of cut flowers held over varying periods of time in the bare hands of menstruating women compared with that of flowers handled by the same person wearing rubber gloves or in the intermenstrual period. Dough kneaded by a menstruating person rose to only half the volume of the control.

<sup>103</sup>Petersen, W. F. and Miller, C. Relation of Menstruation to the Permeability of the Skin Capillaries and the Autoimmune Tissue of the Skin Vessels, Arch. I. Med. 38: 720-725, 1934.

<sup>104</sup>Graham, N. R. and Meyer, V. R. Menstrual Cycle and the Blood Serologic Test for Syphilis, Am. J. Syph. Gonorr. & Ven. Dis. 25: 22-29, 1940.

<sup>105</sup>Schick, H. Das Menstruallongift, Wien klin. Wochenschr. 23: 395, 1910.

On the suggestion of von Gröer Schick<sup>1266</sup> called the hypothetic poison menotoxin. Saenger<sup>1268</sup> in insufficiently reported experiments was unable to confirm Schick's<sup>1266</sup> claim of a menotoxin. He experimented mainly with mice which after the injection of menstrual blood failed to show toxic symptoms. The most interesting part of Schick's<sup>1266</sup> experiments which were in accordance with the popular belief was the toxicity of menstrual blood and sweat to plants. Macht<sup>1267</sup> who had developed a much more sensitive and quantitative phytopharmacological test method confirmed the existence of a menotoxin with well planned and controlled experiments. He together with Lubin<sup>1267</sup> used the length of roots and stems of growing lupinus seedlings and the cultural growth of yeast as indicators. They found a toxic substance present in the serum, blood cells, saliva, sweat and milk of practically every menstruating woman. With their seedling method it was possible to differentiate between the saliva of menstruating and not menstruating women. The hypothesis of a menotoxin (also toxic to small mammals) was later supported by several investigators<sup>1266-1272</sup> but the exact chemical nature of the menotoxin or the menotoxins is not known.

As far back as 1923 Patachke and Sieburg<sup>1272,127</sup> had found that the choline content of the sweat of menstruating women was eighty to one hundred times higher than normal while at the same time in the blood the choline content increased only eight to nine times. These findings substantially confirmed by Klaus<sup>1273</sup> suggest an elective accumulation and excretion of the metabolic toxin in the sweat glands<sup>1273</sup> or its production in the skin. The high choline concentration in the sweat or in the skin may well be one of the causes of menstrual exanthemas.<sup>1273,1277</sup> Macht in more recent studies<sup>1277</sup> suggests that the phenanthrene derivatives cholesterol and oxysterol might be menotoxins. The substances are related to the steroid sex hormones. One also has to consider certain highly toxic substances in the menstrual discharge. Such toxins are formed in the endometrium.<sup>1278</sup> The histamine content of the menstrual blood is much higher (12.5 to 2 000 times) than that of the circulating blood.<sup>1278</sup> Increased activity of the apocrine sweat glands during menstruation is likely. The gonadal relationship of these glands is known. (See Puberty, Menopause.)

The hairdressers claim that permanent waves are not successfully given during the menses but this has not been proved.

<sup>1266</sup>Saenger H. Gibt es ein Menstruationgift? *Zbl. f. Gynäk.* 46: 819, 1921.

<sup>1267</sup>Macht, D. I. and Lubin, D. R. Phytopharmacological Study of Menstrual Toxin, *J. Pharm. & Exper. Therap.* 22: 13-400, 1924.

<sup>1268</sup>Stomessers and Eli. Menstruationgift. *Monatsh. f. Kinderk.* 81: 264, 1923.

<sup>1269</sup>Stomessers, H. Menstruationgift. *München med. Wchnschr.* 81: 1425, 1924.

<sup>1270</sup>Falk, O. W. and Patachke, H. V. Studies on Menstrual Discharge, *Proc. Soc. Exper. Biol. & Med.* 45: 254-257, 1941.

<sup>1271</sup>Macht, D. I. Studies on Menstrual Toxin, *Am. J. Hyg.* 200: 291-303, 1942.

<sup>1272</sup>Colomer, L. A. El síndrome ginecológico de las menotoxinas. *Medicina Española* 11: 302-312, 1944.

<sup>1273</sup>Patachke, W. and Sieburg, K. Zur Ätiologie der Menstruationsexantheme. *Arch. f. Dermat. u. Syph.* 118: 45-62, 1929.

<sup>1274</sup>Sieburg, K. and Patachke, W. Menstruation und Cholinstoffwechsel. *Ztschr. f. exper. Med.* 36: 234, 1923.

<sup>1275</sup>Klaus, K. Zur Frage des Menotoxins. *Blotchen. Ztschr.* 282: 41, 1925.

<sup>1276</sup>Rockman, H. and Orhauf, F. *Chemie d. Haut, Handb. d. H.* 11: 161-377, 1929.

<sup>1277</sup>Wolff, H. and Böhm, A. Acetylcholin und histaminartige Stoffe im Hautdiagnost. *Klin. Wchnschr.* 11: 274-276, 1929.

<sup>1278</sup>Guthrie, H. and Vandell, J. Menstrual Blood Contains Histamine in Notable Quantities, *BoJ. Soc. Nat. Biol. Amer.* 17: 324, 1941.

day of menstruation the next strongest in the midperiod and the lowest on the premenstrual day. Thus the greatest reactivity of the skin would coincide with the period of estrogenic deprivation. The sensitivity to tuberculin has been found greatly reduced during menstruation.<sup>100</sup>

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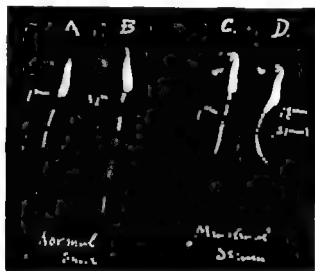


Fig. 301.—Toxic influence of menstrual serum on the growth of seedlings of *Phaseolus albus*. A, root length of roots at the start. B, root after 24 hours in Rhee's solution. C, root after 24 hours in 1 per cent menstrual serum. D, root after 24 hours in 1 per cent normal serum. The root has increased only 4 mm. instead of 15 mm. Normal serum inhibits the growth but not much less. From Nacht D. J. J. (Pharmacol. & Exper. Therap.)

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<sup>100</sup>Petersen, W. F. and Milne, C. Relation of Menstruation to the Permeability of the Skin Capillaries and the Allergic Tonus of the Skin Vessels, Arch. Int. Med. 38: 727-728, 1924.

<sup>101</sup>Isaksson, V. R. and Meyer, V. R. Menstrual Cycle and the Blood Serologic Test for Syphilis, Am. J. Syph. Gonorr. & Ven. Dis. 25: 23-24, 1910.

<sup>102</sup>Schick, B. Das Menstruationsgift, Wien klin. Wochenschr. 22: 395, 1910.

the menstrual cycle. Successful endocrine therapy is an important argument for the hormonal origin of menstrual dermatoses. The increased knowledge of allergy has done much to explain the menstrual repetitions of some skin lesions. As early as 1907 Wolff Eisner<sup>1288</sup> suggested the allergic nature of *menstrual urticaria*. The regularly repeated fluctuations of a great number of substances which may have allergenic qualities and the increased reactivity provide an excellent set up for allergic phenomena. It is to the merit of Geber<sup>1289</sup> to have been the first to demonstrate the allergic character of some menstrual dermatoses. In a case of menstrual urticaria he took serum during the time of menstruation and injected it intravenously into the patient during the intermenstruum. This injection was followed by an outbreak of urticaria while it was not possible to elicit such a reaction with serum taken during the intermenstruum. Menstrual serum from another woman did not work in the patient and the menstrual serum of the patient did not work in another woman. The passive transfer with the method of Praunitz and Kuestner was accomplished and desensitization by means of systematic injections of the autogenous menstrual allergen during the intermenstruum was found to be effective in a considerable number of cases.

Waldboott saw premenstrual urticaria, asthma and sneezing after a severe allergic shock caused by an injection of theelin. This observation is of great theoretical interest but so far the evidence is scant.<sup>1290</sup> Successful desensitization with ultrafiltrate of menstrual blood has also been reported. Menstrual angioneurotic edema is not rare.

The menstrual dermatoses have a definite tendency to recur in the same place as a fixed eruption. This suggests that unknown factors of the terrain play a part in the pathogenesis. It is sometimes possible to change by local X-ray treatment the reaction of such an area and to prevent the recurrence. Since many women take antipyrine for the relief of menstrual symptoms and since antipyrine is known to cause fixed drug eruptions, this possibility has to be considered. It sometimes needs the increased sensitivity of the premenstrual period to produce an antipyrine eruption.<sup>1291</sup> It is of historical interest that the first fixed antipyrine eruption which was described by Brocq in 1904 occurred in a patient who took antipyrine for painful menstruation. The eruption was at first ascribed to her periods (Abramowitz in discussion to Throne<sup>1292</sup>).

In *menstrual urticaria* the eruptions are sometimes confined to the vulva and the surrounding areas. In the typical cases the picture is the same as in nonmenstrual cases of hives.

*Angi neurotic edema* mostly of the lips or eyelids also occurs in connection with menstruation. In one of the author's cases the first attack occurred after

<sup>1288</sup> Wolff-Eisner: Ueber die Urticaria, vom Standpunkte der neuen Erfahrungen Ueber Empfindlichkeit gegenüber körpereigenen Eiweissstoffen, *Dermat.* Bd. 10: 161-172, 1907.

<sup>1289</sup> Geber: II. Einige Daten zur Pathologie der Urticaria menstruationale, *Dermat. Wochschr.* 52: 143-50, 1903.

<sup>1290</sup> Waldboott, G. L. in Dier to Crisp, L. H.: Allergy in Paediatric Thromb. Extr., *J. Allergy* 2: 151, 1941.

<sup>1291</sup> Levy, A., Bureau, Y. and Horowitz, A.: Dermatose catameniales medicamentieuses, *Bull. Soc. franc. dermat. et syph.* 44: 803-805, 1937.

<sup>1292</sup> Throne: B. Erythema menstruale angioneuroticum, *Arch. Dermat. & Syph.* 21: 1034, 1920.

a childbirth and recurred menstrually for twelve years. This type of onset after pregnancy has also been observed in other cases.<sup>1436</sup>

*Menstrual dermatographism* is known

*Pruritus vulvae menstrualis* is not very rare. It is usually taken as a part of the natural congestion of the vulva during the menses and treatment is seldom requested.

### Infections

The menstrual period is accompanied by a lowered resistance to many infections.<sup>1444, 1447, 1448</sup> Many surgeons avoid operations during menstruation because of the increased tendency to inflammatory complications. The self disinfecting power of the skin surface is reduced as shown by Fisher<sup>1449</sup> in systematic investigations with *Bacillus prodigiosus*. The serum of menstruating women shows little or no disinfecting power during the last ten premenstrual days in vitro tests with anthrax bacilli (Drexel and Keller quoted by Geller<sup>1449</sup>). Scarlet fever, diphtheria, tonsillitis and furuncles often start during menstruation. It is known in hospitals that girls admitted because of scarlet fever and diphtheria are usually menstruating.<sup>1444</sup> This general experience was confirmed by a study of hospital nurses. They too were often menstruating when they came down with scarlet fever.<sup>1445</sup> Of 119 women in the menarche almost 50 per cent were menstruating when they entered the hospital having erysipelas. The menstrual character of the infection is more obvious if the outbreak coincides with menstruation more than once. Menstrually recurrent erysipelas is often dealt with in the older literature.<sup>1446</sup> Cases with 50 recurrences of erysipelas have become known. Erysipelas at the time of the expected but absent menses in one case eight times in succession has been recorded. Jerusalem's<sup>1447</sup> observation of eight cases of monthly recurrent erysipelas in males has not been repeated. The whole matter of menstrual erysipelas has during the last twenty five years<sup>1448</sup> found little interest. Premenstrually recurring paronychia has lately been described.<sup>1445</sup> The author saw a case of hidradenitis axillaris which over years recurred quite regularly with the menstruation. In another case a furuncle like deep ulceration of the perineum which took two weeks to heal accompanied many periods.

<sup>1444</sup>Hallbräun, Quinck. *Dermat. und Gynäk. für Emilian*. Marchhagen d. M. 1913. 28  
1913 Abstr. Dermat. Wechschr. p. 1214 1913

<sup>1445</sup>Arnsperg, D. H. The Part Played by Age and Sex in Female Sex Hormones. *Reichsarchiv f. Infektion Endocrinol.* 25: 615-624 1929

<sup>1446</sup>Sprun, D. H. M. Deurman, S. and Raper, J. Sex Hormones and Infection. *J. E. per Med.* 47: 100-64 1929

<sup>1447</sup>Fisher, T. Variations in Self Disinfecting Power of the Skin During the Menstrual Cycle. *Proc. Roy. Soc. Edin. & Med.* 33: 932-933, 1903

<sup>1448</sup>Geller, F. Infektion und menstruelle Zyklen. *Blätterchen med. Wechschr.* 87: 1110 1940.

<sup>1449</sup>Sieyer, F. C. Empfindlichkeit gegen Infektionskrankheiten und Menstrualmenstruation. *München med. Wchschr.* 87: 801 1940

<sup>1450</sup>Horsner, H. Orsbradt, F. and Nordhausen, W. Empfindlichkeit gegen Scharlachinfektion und Menstrualmenstruation. *München med. Wchschr.* 87: 692-693 1910

<sup>1451</sup>Jerusalem, H. Einmalige Scharlachmenstruation bei Erysipel. *Wiener Anz. Med.* 1900

<sup>1452</sup>Stefan, N. Dermatitis Erythematosa Menstrualis. *Verhandl. dermat. u. gyn. 47: 14 1929. Id.*

<sup>1453</sup>74  
<sup>1454</sup>Reichold. Paronychie die sich vor den Menses ereignet. *München med. Wchschr.* 86: 5: 1911

**Menstrual herpes** the infectious nature of which has been established<sup>100</sup> is the most common menstrual dermatosis. About three out of four cases of genital herpes in the female are due to menstruation (Bergh after Steuer<sup>102</sup>). In its appearance menstrual herpes is no different from herpes simplex. After a premonitory burning sensation of a few hours red spots appear which quickly develop into crystalline vesicles. These blisters form one or several small groups. They become pustular after one or two days then they dry up and heal without scars in about one week. The primary blister is quickly destroyed on mucosal surfaces. Here the typical appearance is a whitish or red spot with floating remnants of the blister at the edge. On the skin as well as on the mucosa the blisters may merge to form plaques. The local lymphatic nodes are often tender and slightly enlarged. Next to the genitals the lips and the chin seem to be the most common sites of the eruption. Just as the menstrual acne the menstrual herpes is often seen on the chin. Fournier<sup>101</sup> aptly called this 'herpes indiscret'. Eruptions on the hands on the thighs or elsewhere are much rarer. Unusual and more serious events are menstrual herpes eruptions of the cornea<sup>1007</sup> and of the oral and pharyngeal mucosae. The latter sometimes known as herpetic angina can be accompanied by rather severe constitutional reactions.<sup>1008</sup> The experimental transmission of menstrual herpes into the rabbit cornea has not only been successfully performed<sup>1009</sup> but contact infections in man are known.<sup>1000</sup> Menstrual herpes appears most often immediately before menstruation but in some instances during or after menstruation. The first attacks have been seen to precede the menarche several times in monthly intervals.<sup>1001</sup> It may occur at characteristic intervals in pregnancy<sup>1002</sup> or if actual menstruation is disturbed by disease malformation or aplasia of the internal genitalia.<sup>1003</sup> It may also continue to appear for a short while in the early menopause.

**Menstrual acne** is usually a menstrual flare up of chronic acne lesions. Possibly in connection with an increased premenstrual activity of the sebaceous glands. After the catamenia the acne lesions become dormant again. Nacht<sup>1004</sup> found the menstrual sera of women suffering from acne generally more toxic to seedlings than such sera from women who did not have acne. The blood of young men with acne rarely exerted a phytotoxic reaction. The exacerbation of acne appears in some patients before in others during or after the menstruation often keeping this time relationship remarkably constant.<sup>1005</sup> Some authors claim that the chin is frequently affected by menstrual acne.

<sup>100</sup>Lipchitz, B. Weitere Untersuchungen über die Ätiologie des Zoster. I. Ueber die Mikroscopie der Impfraktion und des generalisierteren Ektzema nach Impfung mit Zoster. Arch. f. Derm. 39: 189 190-206 1923.

<sup>101</sup>Niedermyer, A. Menstruelle Herpesreidivire. Zbl. f. Gynäk. 48: 2681-2684, 1925.

<sup>102</sup>Chavasse, F. Recrudescence Herpétique Anginae. Oto-rhino-laryng. Internat. 25: 572, 1940.

<sup>103</sup>Keisling, Reckl. Recrudescence Herpes simplex menstruelle am 3. und 4. Finger der linken Hand mit erythematöser Anschwellung des Handgelenks und der Ausschwelung des Unterarms. Zbl. 43: 724.

<sup>104</sup>Toussaint, A. Reuss, F. and Pouchgner. Herpes recidivant transmis par un porteur sain de virus. Bull. Soc. Franc. de dermat. et syph. 48: 615 1937.

<sup>105</sup>Reichmann, F. Herpes genitalis. Deutsches Arch. f. klin. Med. 86: 123 207.

<sup>106</sup>Reichmann, F. Menstrual localherpes. Acta dermat.-venereol. 1930 abstr. Dermat. Wchnschr. 71: 572, 1920.

<sup>107</sup>Robinson, B. Herpes as Type of Virulent Menstruation. Dublin J. M. Sc. 4: 117 218, 1821.

**Hemorrhagic Dermadromes**—The hemorrhagic tendency is increased during menstruation and the platelet count is lowered. Menstrual *purpura* of all degrees of severity has been known for a long time. The purpuric lesions may be petechiae or larger hemorrhagic spots. They may be universal or restricted to certain areas e.g. the lower half of the body.<sup>1004</sup> In purpura as in other menstrual rashes there exists a tendency to fixed recurrence. Such fixed purpuric lesions have been seen to recur regularly e.g. around the eyes<sup>1005</sup> or on the thighs.<sup>1006,1007</sup> Menstrual purpuric exacerbation is sometimes observed in conditions which themselves have a hemorrhagic tendency. Menstruation then provides an additional hemorrhagic factor. Cases which allow such an interpretation include one of menstrual purpura in a girl with mitral stenosis<sup>1008</sup> and cases of rheumatic fever.<sup>1009</sup> Here also belongs the case of a petechial menstrual crop on the lower legs which appeared only while a tapeworm was present in the bowel. After removal of the tapeworm the rash failed to appear but recurred menstrually after the recurrence of the taenia. This happened four times.<sup>1009</sup> The bleeding may occur in any open lesion.

Variocoe luetic or other ulcers have often been observed to bleed during menstruation. This phenomenon about which much has been written in the last century has hardly found attention within the last generation. Another type of *menstrual ulcer* improves or heals during the intermenstruum and recurs during menstruation. More often than the menstrual ulcer has the related *vicarious or ectopic menstruation* been studied. In most of the instances the term was used incorrectly since vicarious menstruation should be called only a discharge of blood from some organ other than the uterus with suppression of the menses (Webster). This type has been called substitutional menstrual hemorrhage while for extragenital bleeding of any form occurring together with the bleeding from the uterus the term additional or complementary menstruation should be applied.<sup>1079</sup> This mysterious phenomenon has a history in which early over-estimation was followed by complete denial of its existence during the late nineteenth century. But since then so many observations have been recorded that a reserved but positive attitude has become general. It is well illustrated by a statement credited to Lawson Tait who said that 'he does not deny that there is such a thing as vicarious menstruation but he does deny the propriety of examiners asking the commonest cause of epistaxis and receiving the answer of vicarious menstruation with approval'.<sup>1160</sup>

The nasal mucosa is the most frequent source of vicarious bleeding. This is not surprising since menstrual swelling of certain areas of the mucosa covering

<sup>1004</sup>Jobs. *Purpura dysmenorrhoea*, Zbl 48 291 1933

<sup>1005</sup>Beverman, H. A Case for Diagnosis (Cutaneous Vicarious Menstruation? Hysteria?) Arch. Dermat. & Syph. 33 760-780, 1935.

<sup>1006</sup>Hirschberg, A. Ueber die Beziehungen der Menstruation zur Bl. (Zbl f. Gynäk. 48 1906-1907 1921)

<sup>1007</sup>Haider. Prämenstruell reaktivierendes, & an Ekzem nach Salvarsantherapie (M. 33 418 1934)

<sup>1008</sup>Winkler F. Menstruelle Ekchymosen durch Darmparasiten hervorgerufen. Dermat. Wchnschr 61 482 1917

<sup>1009</sup>Casati, W. H. Complementary (Vicarious Ectopic) Menstruation. *Gynaecologia, Mammae, Vero* Am. J. Obst. 72 224-231 1916

the lower turbinates and the tuberculum was long ago observed by Fliess,<sup>14</sup> who found these areas during menstruation invariably swollen hypersensitive and apt to bleed on the slightest touch.

While ectopic menstrual bleeding from the gastrointestinal canal, the lungs and the mammary glands have been observed relatively often, sometimes under alarming circumstances, the skin seems to be a rare source. Condit<sup>144</sup> saw a hematoma of hen's egg size develop from a small nevus on the chest in menstrual intervals after the uterus and the adnexa had been removed. After excision of the nevus hemorrhage in the breast occurred. Other reported sources of vicarious menstruation include old scars, endometriomyoma of the umbilicus<sup>145</sup> the nailbeds, the lips and gums. Bleeding from fistulae, cancerous lesions and hemorrhoids must be interpreted in the same way as the menstrual ulcer.<sup>143,147</sup>

The menstrual history of these cases often reveals irregularities. Puberty and still more the approaching or beginning menopause seem to predispose. Several cases have been observed after hysterectomy.<sup>148</sup> Since extravasations are among the manifestations of hysteria, it is not surprising that psychopathic individuals are often found among the afflicted. For the sake of curiosity a twenty-four-year-old male sexual psychopath with unusual psychic attachment to his mother may be mentioned.<sup>149</sup> He developed monthly cutaneous extravasations in his right arm pit.

### Erythemas

Besides such clinically well-characterized menstrual dermatoses as herpes, urticaria and purpura a great variety of transitory menstrual erythemas have been observed. The simplest form is the noninflammatory erythema of the face which sometimes marks approaching menstruation. It seems to be a first step towards rosacea which has a marked gonadal relationship (see Rosacea). Occasionally the congestion may involve the conjunctiva.<sup>150</sup> In some cases rosacea starts as a menstrual erythema in the 'blush' area and becomes a stable erythema during the menopause. Some menstrual erythemas have the characteristics of erythema exudativum multiforme with nummular papulo-erythematous lesions on the face, neck, forearms, and lower legs. Some are more vesicular and some show a small vesicle in the center of the red lesion. Typical are the herpes-like forms while gyrate or erythema nodosum-like lesions are not extremely rare.<sup>151</sup>

There is a tendency to fixed eruption. More rarely the appearance is vicarious, appearing only at the time of the missed menstruation. Some of the cases which have been described as menstrual erysipelas probably belong to the erythemas. In some cases tonsillectomy<sup>152</sup> or staphylococcal vaccine cured menstrual crops of erysipelas-resembling erythemas.

<sup>144</sup> Fliess: Beziehungen zwischen Nase und weiblichen Geschlechtsorganen, Leipzig, 1907.

<sup>145</sup> Exner: V. Endometriomyoma of the Umbilicus, Arch. Path. 28: 478-486, 1930.

<sup>146</sup> Hadley & E. Ashbury: Menstruation in Male Am. J. Psychiat. 9: 1101-1111, 1930, Ed. 28: 142, 1931.

<sup>147</sup> Schaefer: D. Fälle von Toxidermia menstruale mit erysipeloidartigen Eruptionen, Magy. Xbryter 8: 199-201, 1936, Ed. 64: 614.





Fig. 205.—Menstrual eruption resembling erythema multiforme



Fig. 206. Fixed menstrual eruption of vesimaculose character revealing almost entirely dark in coloration

Miscellaneous.—Menstrual *chromodrosis* of which substantiated reports can be found in the older literature<sup>100</sup> has not been heard of during the last fifty years. It seems that the discolorations of the sweat either were feigned or caused by staining substances from without and not by excreted indigo as had been suggested. *Bloody sweat* has several times been seen in menstrual attacks. It is a hemorrhagic phenomenon of the same significance as other purpuric symptoms.

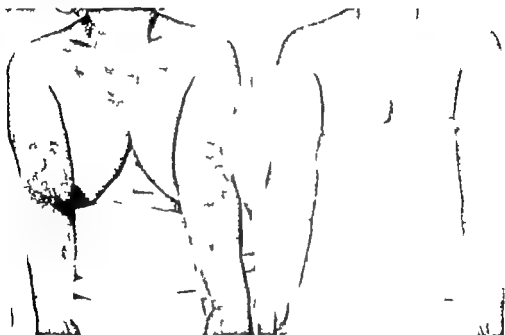


Fig 207.

Fig 208.

Fig 207.—Menstrual dermatitis. From Urbach, H. *Allergy* Grune & Stratton, Inc.)

Fig 208.—Eczema patches in intermenstrual m. (From Urbach, H. *Allergy* Grune & Stratton, Inc.)

The menstrual darkening of freckles, of the linea alba or of other *pigmentations* is occasionally quite marked. The greater pallor of some menstruating women or a rudimentary chromatophoric function of the anterior pituitary may be suggested as an explanation. No recent investigations have been published. Rühl's<sup>101</sup> observation of menstrual discoloration from gold jewelry has not found much confirmation. Naturally one has to think of silver sulfides developed in more visible amounts by increased menstrual sebaceous secretion. Menstrual soreness of the mouth and aphthous ulcerations may become quite troublesome. In some cases these eruptions can be prevented by theelin.<sup>102</sup>

<sup>100</sup>Heldmann, M. and Andersen, B. G. Oral Manifestations of Certain Systemic Disorders. *Yale J Biol & Med* 17: 552-561, 1912.

*Treatment*—In all menstrual eruptions correction of any hormonal disorder should be tried. Sometimes the eruption fails to recur if normal menstruation can be restored. But this is not always true. In some cases menstruation is normal except for the rash but the rash may yet be cured by theelin<sup>122</sup>. Not only theelin but theelin in the first half of the intermenstruum and progesterone in the second half has been given successfully (Urbach<sup>97</sup>). Other hormones or combinations of hormones e.g. a placenta preparation and dried adrenal glands<sup>123</sup> have occasionally helped.

A method of treatment which should be tried in all refractory menstrual eruptions is Geber's desensitization to premenstrual blood<sup>124</sup> which has been successful in a considerable number of cases. Urbach<sup>97</sup> describes the technique as follows. About 20 c.c. of blood is taken at the acme of the premenstrual exacerbation. There is some difficulty in determining the right time since much seems to depend on getting the most potent allergen. The blood is centrifuged and the serum poured into a rubber capped bottle. After 1:10,000 of merthiolate has been added the serum is stored under refrigeration. Then 0.2 c.c. of serum is injected intracutaneously every second day. The injections are given four successive times into the same site. The site of injection is changed after eight to ten days. Lehner and Rajka (after Urbach<sup>97</sup>) inject 0.4 c.c. daily into two areas in corresponding symmetrical sites. While this method was originally used in menstrual urticaria it later proved to be effective in other menstrual dermatoses and complications also e.g. in menstrual trigeminal neuralgia.<sup>125</sup>

<sup>122</sup>Adrenal Substance in Dermatoses Which May Have Menstrual Factor Arch. Dermat. & Syph. 31: 265, 1935.

<sup>123</sup>Geber H. Desensibilisationsversuche bei Menstrualen exzacerbationen, Med. Klin. 31: 1203-1204, 1935.

## CHAPTER XXIII

### PREGNANCY

The fertilized ovum after its implantation into the uterine mucosa causes profound changes in the hormonal balance. Within a few days after the first missed period the anterior pituitary like hormone (chorionic gonadotropin) from the placenta increases in the blood as well as in the urine and reaches a level many times higher than normal after about sixty to ninety days. This peak subsides and remains at a lower but still elevated level until delivery. The estrogen content of the blood and urine increases progressively from the second month until near term. The progesterone level rises until after the fifth month when the corpus luteum undergoes involution. The ratio of the estrogens changes and may assume an abnormal pattern in pre-eclampsia.<sup>123</sup> With the expulsion of the fetus and placenta a rapid return to the pregravid state ensues with a slump in the normal production of hormones.<sup>124</sup>

It is natural that the hormonal upheaval of pregnancy is associated with profound changes in the entire endocrine system.

The anterior lobe of the *pituitary* increases to two and one-half times its usual weight and there are characteristic microscopic changes. The large amount of pituitary gonadotropic hormone in the blood and urine is well explained by this hypertrophy. This may account for various stimulations of growth of the skin and its appendages.

After the third month the *thyroid* gland increases in size in almost all cases and its activity is stepped up. Iodine moves from the thyroid into the blood reducing the glandular iodine level about one half. The basal metabolic rate is often raised. If the thyroid is unable to meet the increased demand for thyroxin hypothyroidism may develop. The hyperthyroidism of pregnancy may explain certain sensations of heat, hyperhidrosis and erythema.

The *parathyroid* glands too are stimulated probably due to the high demand for calcium for the child's skeleton. The calcium deposits in the mother are drained. The blood calcium level is lowered. Inability to meet the increased requirement may cause a state of hypoparathyroidism with tetany. The ovaries swell and the follicles continue to develop but fail to ripen. The *corpus luteum* *verum* provides an uninterrupted supply of progesterone needed for implantation, the prevention of uterine contraction and the formation of the decidua. After the first half of the pregnancy the corpus luteum undergoes involution to prepare the termination of pregnancy. Some of its functions are taken over by the pituitary and the placenta. The increased secretion of estrin changes the microscopic picture of the vaginal smears. The epithelial cells increase in size during the first months. Later they become smaller again so-called oyster-shaped cells appear and leukocytes abound. Just before labor the desquamation of the

vaginal mucosa almost reaches denudation. The adrenal cortex hypertrophies during pregnancy to meet the greater demand. That the demand is greater has been shown by the fact that adrenalectomized cats need more cortical extract for survival during pregnancy than when nonpregnant. The lowered glucose tolerance of pregnancy is perhaps caused by a hyperactivity of the adrenal medulla though it has been ascribed to pituitary, pancreatic, liver and renal factors. In the liver glycogen disappears from the central portion of the lobules and bile stagnates in the biliary channels.

During the latter part of pregnancy a great amount of nitrogen is stored in the maternal system beyond the need of the fetus. The blood N P N falls. Albuminuria is common.

The fat content of the blood increases after the third month giving the blood serum a cloudy appearance. The alkalinity of the blood is increased. Cholesterol is increased in the blood and in the adrenal glands. The blood cholesterol (not the cholesterol esters) increases about 100 per cent.<sup>121</sup> There is a retention of sodium, potassium, magnesium and sulfur and the excretion of iron and phosphorus is decreased. The retention of most of the minerals exceeds the needs of the growing fetus.

**Normal Skin Changes.**—The skin responds to pregnancy in many ways. According to the majority of the observers the perspiration is increased especially towards the end of the pregnancy. Extreme degrees of hyperhidrosis have been seen<sup>122</sup> in this period. The increase of sweat secretion may take some strain off the kidneys. The urea may rise in the sweat with increasing renal insufficiency. Chlorine increases in the sweat during the first half of the gestation but decreases later. In toxemia it is greatly reduced.<sup>123</sup> Prolan appears in the sweat of the pregnant women.<sup>124</sup>

An actual hypertrophy of the sweat glands which had been claimed earlier<sup>125</sup> does not seem to have been confirmed in more recent investigations. It has been suggested that the growth of the sweat glands in pregnancy is part of the acromegalic tendencies caused by the pituitary changes.<sup>126</sup> The perspiration insensibility decreases with the progress of the gestation but increases during the puerperium. The loss of water through the skin is particularly low in toxemia.<sup>127</sup>

The apocrine gland, the gonadal relationship of which has been mentioned in the chapter on Puberty, probably cease to secrete during pregnancy.<sup>128</sup> The secretion of the sebaceous gland increases during the latter half of gestation.

<sup>121</sup>Marshall F. Der Lipidstoffwechsel. *Erbh.* 28: 1-32, 193-312, 1930.

<sup>122</sup>Pauli E. II peridrome gravidarum. *Erbh.* 1: 129-134, 1902.

<sup>123</sup>Leitch E. The Vile Signs of Excretion in the Toxemia of Pregnancy. *Am. J. Obst. Gynec.* 87: 273-280, 1923.

<sup>124</sup>Leitch E. Le prolane dans le sueur de la femme enceinte. *Am. J. Obst. Gynec.* 88: 10-13, 1923.

<sup>125</sup>Reichardt. Nach Versuchsversagen in der Arch. gynecol. Monat. Ber. 1911.

<sup>126</sup>Glaser. Über die Bedeutung von Hautveränderungen bei den Abweichungen der endokrinen Drüsen. *Erbh.* 22: 1-11, 1923.

<sup>127</sup>Palmermacher L. Hautveränderungen bei der Akromegalia bzw. auch bei der Hypothyreose in ihrem Zusammenhang mit der innersekretorischen Tätigkeit der Kribsdrüsen. *Arch. f. Frauenk.* 8: 2-11, 1923.

<sup>128</sup>Pauli E. Die Arch. gynecol. Monat. Ber. 1911. *Obstet. u. Gynäk.* 1: 11-13, 1902. *Pathol.-anat. Histologie u. Pathologie des Weibes* ed. 7 Berlin 1927. Urban & Schwarzenberg p. 192.

This seborrhea is especially marked during the last five days<sup>100</sup> and during labor. Soon after delivery both hyperhidrosis and seborrhea return to normal. It is interesting that the seborrhea of pregnancy is only rarely accompanied by acne.<sup>101</sup> Usually existing acne is improved. This suggests that not seborrhea but other factors (comedones) are the cause of juvenile acne.

*Implantation of particles of normal skin* of pregnant women into rats and infantile mice produces the same changes as the pregnant woman's urine. It does not elicit the Allan Dowsy reaction. This proves that prolactin and not estrogen is the active principle. The prolactin is apparently stored in the skin. Skin which has been rendered anemic is not less and skin with the pigmentation of pregnancy is not more effective than normal skin.<sup>102</sup>

The epidermal mitoses are more numerous in pregnancy at least in the guinea pig.<sup>103</sup> This indicates a stimulated growth which manifests itself in an occasional thickening of the skin in hypertrichosis and in the development of small neoplasms. The lips may appear thicker, the features coarser and the facial expression may well resemble an early stage of acromegaly.

**Pigmentation**—During pregnancy certain areas of the skin which already have a tendency to increased pigmentation receive a stimulus to produce more pigment than in the nonpregnant state. Scars particularly those from abdominal operation often take part in the pigmentation. Brunettes become much more heavily pigmented than blondes. Generalized melanosis and darkening of larger but circumscribed areas adjoining the well known physiological sites of pigmentation although a little more common in pregnant hyperthyroid women<sup>104</sup> is extremely rare. The *linea alba* or more correctly the midline of the abdominal skin usually becomes pigmented in the third month of pregnancy but sometimes much later especially in blondes and multiparae.<sup>105</sup> This *linea fusca* or *linea nigra* as it is often called extends from the mons veneris to the navel and though less often and less pronounced into the epigastric region. The line is about one third of an inch wide and varies in color from light greyish brown to deep brown or black. If it extends to the epigastric area it often forms a one half to one inch wide brown ring around the navel which is called the umbilical areola of Montgomery. The black line is present in 94 per cent of pregnant women. It is occasionally missed in obese women and in very light individuals rarely in the darker pigmented women. The pull of the ligamentum teres of the liver sometimes causes a deviation to the right of the supraumbilical part thus producing a bayonet-shaped line.

The areolae of the mamillae darken more intensely than the *linea nigra*, the degree varying again with the color of the hair. There is a certain amount of darkening around the areola proper. This "secondary areola" consists of a network of brownish lines surrounding the lighter follicles. The secondary areola

<sup>100</sup> Florin M. La seborrhée observée in gre idamee, Arch. di se biol. 27: 71-80, 1922.

<sup>101</sup> Wolff L. Ach. sauerstoffaufnahme und Haut, Zbl. 27: 22, 1922.

<sup>102</sup> Langer A. Die Haut als Hormonträger in der Schwangerschaft, Zbl. f. Gynäk. 54: 1125, 1922.

<sup>103</sup> Lamb, L. and H. von P. L. The Relation Between States of the Sex Organs in the Female

Guinea-pig and the Cell Proliferation in the Epidermis, Anat. Rec. 43: 136, 1929.

<sup>104</sup> Eusebio O. La pigmentación a type adisonica dans la maladie de Basedow. Rev. franc. d'endocrinol. 6: 190-206, 1923.

though being a sure symptom of pregnancy does not appear before the fifth month.<sup>1001</sup>

The hyperpigmentation of the vulva can reach extreme degrees. The edges of the labia minora are intensely pigmented. The discoloration may



Fig. 209. Melanosis of pregnancy. Note deviation of pigmented line alba to the right caused by pull of ligamentum ciliare superius. Courtesy Division of Dermatology, Department of Medicine, University of Chicago.

extend beyond the vulva to the perineum to the inner aspects of the thighs and around the anus. Rarely old scars and striae become pigmented. The sensitivity to light increases in pregnancy which causes more ready tanning.<sup>1007</sup>

The number of noticeable pigmented spots increases in about 25 per cent of the pregnant women. Freckles or lentigo-like spots appear or become more pronounced.<sup>1002 1003</sup> An unpigmented mole may become pigmented.

<sup>1001</sup>Karrer, E., I. Halban, J. and Retzi, L. *Biologie und Pathologie des Weibes*, vol. 8, Berlin, 1928, Urban & Schwarzenberg, pp. 784-789.

<sup>1002</sup>Jordan, A. *Albinismus faciei bei jungen Mädchen, nichtschwangeren Frauen und Männern*, *Dermat. Weekblad* 94, 236-240, 1933.

<sup>1003</sup>Goldschmidt, W. N. *Pigmentation Brit. J. Phys. Med.* 25, 42-46, 1930.

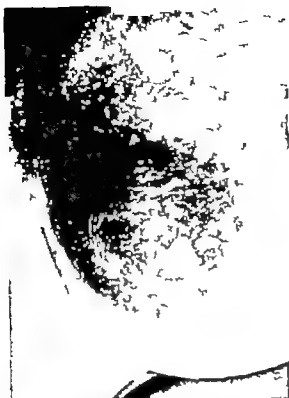


Fig. 310 — Pigmentation of breast in pregnancy



Fig. 311 — Chloasma, persisting after pregnancy. Irregular menstruation.



"Quae utero gerunt in facie maculam habent" Those who are pregnant have spots on the face. This was known as a fact to Hippocrates but in the nineteenth century<sup>180</sup> the connection of *chloasma* with the uterus was still the subject of much controversy. It was either claimed that it had nothing to do with the uterus or that it was identical with *tinea versicolor*. *Chloasma* is present in 74 per cent of all pregnant women in the later part of the gestation. Only one third of the cases are marked; the rest are more often pale than pronounced depending much on the color of the skin and hair. (F. A. Kehrer and Karl Hoffner after E. Kehrer<sup>184</sup>) The color may be deepened by exposure to light.<sup>184</sup>

The *chloasma* of pregnancy consists of sharply outlined, often jagged yellow, brown or grayish spots. They are symmetrical and follow certain patterns.<sup>185</sup> They either appear as scattered small spots on the cheeks and nose or as a mask like discoloration which leaves the lids, the surroundings of the eyes, the preauricular areas, parts around the mouth, the temples and almost always a narrow strip along the frontal hairline free. In another type the temples and the zygomatic areas are dark while a trapezoid area in the center of the forehead remains light.<sup>186</sup> Transitional types between these patterns occur.

*Chloasma* usually disappears within a short time after delivery. The first menstruation seems to stimulate the bleaching. Not infrequently the spots fail to vanish for a long time even for many years. *Chloasma* has even been seen to persist in the menopause. (Muratori after Sézary and Duray<sup>186</sup>)

*Chloasma*-like pigmentations are not exclusively seen in pregnancy. They have been observed in young girls, nonpregnant women and in men. *Chloasma periorale virginum* is a type of stubborn *chloasmatic* pigmentation in the lips of young girls.<sup>187, 188</sup> The nonpigmented narrow strip separating the *chloasma* from the vermillion border which originally was described as characteristic in this condition can be seen in many perioral pigmentations, e.g. in perioral vitiligo.

The pigment of pregnancy is melanin. As such it is iron free<sup>189</sup> and in its histological characteristics is no different from melanin deposits in other condition.

The cause of the pigmentations of pregnancy is seen by some authors in the adrenal cortex hypertrophy.<sup>190, 191</sup> There is no doubt about the existence of adren. changes in pregnancy and about the connection of pigmentations with the adrenals, but it has not been proved that just the pigmentations of pregnancy

<sup>180</sup>Ulrich, H. E. Schwangerschaftspigmentierung und Chloasma. Handb. d. H. 11. 4. 2. 900. 1932.

<sup>181</sup>Forster, J. Formen und Ursachen der als Chloasma bezeichneten Brown- oder Hyperpigmentations des Gesichtes. Derm. Ztschr. 88. 14-19. 1930.

<sup>182</sup>Sézary, A. and Duray, A. Melasma. Nouvelle pratique dermatologique. 10. 6. Paris. 1936. Malassez & Co. pp. 825-427.

<sup>183</sup>Ulrich, H. E. Chloasma periorale virginum. Folia. 184. 11. 17. 1934.

<sup>184</sup>Forster, J. Histologic and Histochemical Study of Pteridosis in Pregnancy. Arch. f. Gynäk. 189. 323-340. 1933.

<sup>185</sup>Grunwaldt, H. and Grubisberg. Ursache und Bedeutung der sich answachsenden pigmentationen. Ztschr. f. Geburtsh. Gynäk. 88. 734-76. 1933.

<sup>186</sup>Ulrich, H. E. Les dermatoses au développement et les affections cutanées de la grossesse. Gynéc. M. Obst. 31. 44-72. 1930.

are caused by the adrenal influence. It has been shown<sup>189, 190, 191</sup> that in animals as well as in man pigmentations identical to those in pregnancy can be produced by the implantation of ovaries or by the injection of large amounts of estrogen under certain conditions. In pregnancy there exists a tremendous increase of the estrogen level. The work of Bloch has so far given the best explanation for the pigmentations of pregnancy. The pregnancy of one of a pair of Siamese twins provided a unique observation. The nonpregnant twin developed chloasma as well as the pregnant one. Both chloasmas were concordant. (Hübner after Meuwsky<sup>184</sup>) This proves a hormonal or humoral cause of the pigmentation and at the same time the existence of certain local possibly hereditary factors necessary for pigment formation. A hereditary factor in chloasma uterinum without pregnancy is established<sup>177</sup>

It has been suggested that the vitamin C deficiency in pregnancy may have something to do with chloasma. Vitamin C is known to exert an inhibitory influence on melanin formation at least under experimental conditions (see Addison's Disease). However it has not been established that prophylactic administration of Vitamin C in pregnancy prevents or heals chloasma.<sup>192, 193</sup>

Statistical and untometric investigations in a large number of pregnant women<sup>194</sup> seem to corroborate the belief that heavy pigmentation is associated with an undisturbed pregnancy. It is statistically correlated with less vomiting, vigorous labor and less danger of atonic hemorrhage and perineal lacerations. On the other hand Grossmann and Schöneberg<sup>195</sup> based on laboratory studies deny any metabolic differences between heavily pigmented and nonpigmented pregnant women and attach no diagnostic or prognostic value to this phenomenon.

**Hypertrichosis.**—Occasionally the hair growth of the face and some other areas increases considerably during pregnancy. This was already known<sup>143, 164, 196</sup> when Halban<sup>164</sup> (1906) discovered that hypertrichosis is a physiological phenomenon of pregnancy. It is ordinarily so slight that it passes unobserved. The light down on the face<sup>197</sup> as well as on the arms, legs and the abdomen becomes a little heavier and darker. Along the linea nigra it may or may not lead to a

<sup>189</sup>Lipowitz, A. Über den Ort der Pigmentbildung. *Virchows Arch. B path. Anat.* 278: 678-680, 1930.

<sup>190</sup>Bloch, B. and Goldberg, D. Die Ursache der Schwangerschaftshyperpigmentierung. *Klin. Wchnsch.* 53: 724-725, 1933.

<sup>191</sup>Bloch, D. Erzeugung der Schwangerschaftshyperpigmentierung (Chloasma, Linea alba) beim Menschen durch Injektion des Ovarialhormons (Oestrogendel). *Klin. Wchnsch.* 49: 16, 1932.

<sup>192</sup>Bloch, D. Über hormonale Beeinflussung der Pigmentbildung. *Klin. Wchnsch.* 44: 219, 1933.

<sup>193</sup>Payson, T. E. Sex Hormones and Hair Changes in Rats. *Endocrinology* 20: 458-464, 1942.

<sup>194</sup>Teicher, F. Chloasma gravidarum und Vitamin C. *Klin. Wchnsch.* 22, II: 1616, 1954.

<sup>195</sup>Grossmann, H. Chloasma gravidarum—Vitamin C. *München med. Wchnsch.* 94: 1226-1237, 1957.

<sup>196</sup>Yoshikaki, S. Studies on Skin Pigmentation During Pregnancy. *Jap. J. Obst. & Gynec.* 11: 241-243, 1932. *Klin. Wchnsch.* 31: 63. *Jap. J. Obst. & Gynec.* 12: 805-870, 1939. *Klin. Wchnsch.* 34: 293. *Jap. J. Obst. & Gynec.* 12: 374-377, 1940, 1939. *Klin. Wchnsch.* 30: 236.

<sup>197</sup>Johnson, A. Case of Hirsuties Gestationis. *New York M. Rec.*, 1878.

<sup>198</sup>Hilgar, A. Zur abnormen Behaarung Before u. Geburt. *Gynaek.* 4: 51, 1901.

<sup>199</sup>Halban, J. Über ein bisher nicht beobachtetes Schwangerschaftssyndrom (Hypertrichosis gravidarum). *Wien Klin. Wchnsch.* 19: 1806, 20: 1807.

<sup>200</sup>Reverez, A. Hypertrichosis superciliaris et la fronte la gravidita. *apertus, Acta dermat. venerol.* 29: 784, 1930.



Fig. 212 —Hypertrichosis of pregnancy (From Stoddard, F. J. Am. J. Obst. & Gynec. 1915)



Fig. 213 —Same patient, shown in Fig. 212 4 months after delivery. Hypertrichosis hair as so marked in pregnancy has completely disappeared. Eyebrows appear less heavy (From Stoddard, F. J. Am. J. Obst. & Gynec. 1915)

pronounced male type of hair distribution.<sup>183</sup> Occasionally a marked hair growth appears just in the midline quite different from the male distribution. Halban<sup>184</sup> showed that two weeks after shaving the abdomen of a pregnant rabbit was covered with thick hair while hardly any growth could be noticed in the controls. It took less than half the time to restore the full hair of a pregnant rabbit than was necessary in the nonpregnant. Similar observations have been made in other domesticated animals. However the increased growth stops before the parturition.<sup>184</sup> The hypertrichosis of pregnancy usually disappears shortly after delivery and sometimes at the time of the first menstruation but it may reappear in subsequent pregnancies. It is suggestive to relate the hypertrichosis of pregnancy to the hypertrophy of the adrenal cortex. Pituitary and thyroid stimulation may play a part.

A pregnancy test based on the sulfur content of the hair compared with that of nonpregnant women has been described by Kosulakoff.<sup>185</sup> It has not found enough confirmation.

Alopecia areata has a tendency to disappear in pregnancy but may recur shortly after parturition.<sup>186</sup> In some cases alopecia areata began shortly after pregnancy. A seemingly paradoxical and rare phenomenon is the disappearance of hypertrichosis of the upper lip during pregnancy and its recurrence after parturition.<sup>186</sup>

The daily growth of the nails during pregnancy has been found to be increased from 0.13 to 0.16 mm.<sup>187</sup>

**Striae, Including Those Not Related to Pregnancy**—Striae are stripe-shaped lesions which by their form and arrangement across distended skin immediately show that mechanical tension is a factor in their pathogenesis. Though by far most common in pregnancy they occur in other conditions in most of which the skin is or has been under mechanical strain caused by enlargement of the volume of tissue which it covers.

Since the striae of pregnancy are the most common example of striation the whole phenomenon may be discussed in this chapter. The striae of pregnancy are linear or somewhat wavy stripes of one to 1½ inches (2.5 to 13 cm.) in length and one quarter to one half of an inch (0.6 to 1.2 cm.) in width. Fresh striae are deep pink or purple the latter color not being due to hemorrhage as one might expect but to the transparency of the thinned skin. In the early stage they look like the marks of whip lashes which in French are called *vergetures*. This expression is occasionally used for striae. Gradually the thin transparent skin is replaced by a denser scar-like tissue of pearly white color. Sometimes old striae are brown with pigment. Striae never disappear completely but they may

<sup>183</sup>Stockard<sup>183</sup> found the 17-ketosteroid levels in one of his cases to be 3.2 to 12 mg. in the twenty-four-hour urine compared with the normal pregnancy range of 3 to 6.5 mg.

<sup>184</sup>Stockard, P. J. *Hirsutism in Pregnancy*. *Am. J. Obst. & Gynec.* 49: 417-422, 1945.

<sup>185</sup>Howell. *Hypertrichosis in Pregnancy*. *Starb. f. d. ges. exper. Med.* 104: 122, 1934.

<sup>186</sup>Alamandusky, K. M. *Le diagnostic de la grossesse au debut par la réaction chimique des cheveux*. *Gynecologia (Accouchement)*, p. 24, 1934.

<sup>187</sup>Lombart, B. *Hypertrichosis an der Oberlippe und der Schenkel während der Gravidität*. *Klin. Wochenschr.* 11: 1037-1038, 1934.

<sup>188</sup>Halban, J. and Spitzer, M. K. *Ueber das gesteigerte Wachstum der Nägel in der Schwangerschaft*. *Monatsschr. f. Geburtsh. Gynäk.* 82: 33-31, 1939.

become quite inconspicuous. The surface of fresh striae is smoother than the normal skin sometimes slightly wrinkled transversely or diagonally so that diamond-shaped figures are formed

Fig. 214



Fig. 215

Fig. 214. Striae of pregnancy

Fig. 215. Old atrophic striae of pregnancy

The palpating finger receives the impression of emptiness and decreased resiliency. This is caused by the lack of the elastic fibers the skin skeleton. Some striae on the lower abdomen and the sides are raised and more palpable.<sup>334</sup>

The striae caused by pregnancy are usually but not always, symmetrical. They are arranged in several groups. One group of longitudinal striae surrounds the navel extending farther downward than upward. A second less pronounced system occupies the lower abdomen its striae often crossing those mentioned before. A third system runs longitudinally over the hips down to the thighs. A fourth large group forms concentric and approximately circular figures around the sacral area. This group may extend upward as far as the eighth dorsal vertebra. Other mostly smaller bunches may surround the popliteal and elbow areas and cover the shoulders and axillary folds. Their direction is longitudinal. Finally the breasts show striae arranged in radial fashion around the areola.<sup>335</sup>

<sup>1892, 1893, 1894</sup> It should be kept in mind that striae are not always caused by pregnancy. This fact is occasionally of some forensic importance. Striae from obesity are mostly found in longitudinal groups on the upper arms, hips, and thighs. Some surround the navel. The striae produced by fast growth during adolescence run transversely. They cross the thighs and to a lesser extent the hips and the lower back. The striae following typhoid fever, dysentery and other infections are most frequently found across the lower thighs just above the knees. Generally striae develop in a direction perpendicular to the maximal tension. If a limb grows longer the striae appear transversely. If it increases in thickness the striae are directed longitudinally. Irregular tractions produce irregular striae e.g. those one observes occasionally on the side of the chest opposite to a pneumothorax.<sup>336</sup>

Striae gravidatae occur in at least 90 per cent of all pregnant women though in very different degree (Credé and many other authors after E. Kehrer<sup>337</sup>). These high figures were derived from observations on white European women. Some but not all pigmented races for instance the women of Java and the negroes of West Africa are reported to develop striae only very rarely.<sup>338</sup> This may be partly due to racial peculiarities or to the massaging of the pregnant abdomen a custom which has found its advocates in the western world.<sup>339</sup> Barfurth claimed that fifteen to thirty minutes of daily gentle kneading of the abdominal skin prevents formation of striae. This treatment is also supposed to bring about a better contraction of the abdomen after delivery. The recommendation does not seem to have been widely followed.

The histology of the striae shows that the lesion is situated in the deeper layers of the cutis. There is a marked basophilic reaction and changes in the shape and texture or complete atrophy of the elastic fibers within the striae and an increase in the pathological fibers at the border of the lesion. Here some of them look

<sup>334</sup> Fontana, B. Pregnancy Complications—Arophic Striae. Ann. d'ostet. gynec. 61: 1245-1251, 1859.

<sup>335</sup> Järnström, A. B. Atrophien der Haut. I. Arzt und Ziefer. Die Haut und Geschlechtskrankheiten d. H. Berlin, 1903 (Urban & Schwarzenberg, pp. 718-721).

<sup>336</sup> Oppenheimer, H. A ruphien. Handb. d. H. u. Gk. 8, 3: 800-7 a, 821.

<sup>337</sup> Coumb, J. L. Cas de vergetures thoraciques unilatérales. Bull. et mémo. Soc. méd. d'Hôp. de Paris 43: 008, 937.

<sup>338</sup> Gurin, C. B. Ueber Schwangerschaftsstreifen, Zbl. f. Gynäk. 38: 431, 1912.

curled as if they had given way to the tension and snapped back. Inflammation has occasionally been noticed in the early stages. Like the blood vessels they are arranged in the direction of the tension. It seems as if the tension does much harm to the elastic and only little to the collagenic fibers. The microscopic findings can be interpreted as evidence of chemical as well as mechanical damage to the elastic fibers. Lately Fontana<sup>100</sup> has described striae with a marked inflammatory reaction and lack of distention as expressed by the normal wavy appearance of the papillae.

The microscopic evidence furnishes some support to the opinion of the majority of modern authors that the mechanical tension however necessary it may be is *not the only factor* in the pathogenesis of striae. This belief is based on a variety of observations. Some pregnant women develop striae in spite of relatively little tension others never do no matter how extended their abdomens become. Of possible significance is the case of a pregnant woman who acquired striae over the biceps muscle of one arm from carrying books while the same exertion did not cause striation when she was not pregnant.

Tension does not always lead to striae. There are many cases of enormous cysts, ascites and edema with extreme stretching of the skin but without striae. While the fat boys with Fröhlich's syndrome rarely show striation the obese patients with Cushing's syndrome always have them and just in this condition the striae not only are the widest ones one can observe but they are already very marked when obesity has not reached degrees which could easily explain cutaneous tears. In men striae are found in 6 per cent.<sup>101</sup> Men are probably less apt to develop striae than women if one does not consider the striae of pregnancy. The pronounced striation in the basophile adenoma of the anterior pituitary and the pituitary changes in pregnancy suggest a pituitary hormonal factor. Pseudoxanthoma elasticum which is clearly a disease of the elastic fiber has been seen appearing in crops during two pregnancies of a patient.<sup>102</sup>

The loosening effect of pregnancy on the elastic tissue of the pelvic ligaments which is said to be of pituitary origin may be caused by the same agent which has an affinity to the elastic fibers of the skin. The kyphosis which commonly develops in Cushing's syndrome may also be due to the same elastic loosening factor as the striae. In the cases of striae caused by adolescent growth the actual tension of the skin is not great compared with other conditions of stretched skin which do not lead to striation. Adolescence is a period of increased pituitary activity. Infection too may have a damaging influence on the elastic fibers. Striae are known to occur though only in a small minority of the patients, mostly adolescent, after typhoid fever, dysentery, paratyphoid in the course of typhus, rheumatic fever, leprosy, syphilis and other infections. Almost always the patient have been bedridden over a long period of time. In these cases the striae are found on the back and often above the patella which may have something to do with lying in bed with the knees bent. In pulmonary tuberculosis

<sup>100</sup>Olafronke, A. Contribution à l'étude des végétations lésionnelles, Ann. d. dermat. et syph. 8: 733-734, 1917.

<sup>101</sup>Kleiner, E. Pseudoxanthoma, luesium and Graviditas, Zbl. 19: 3, 1923.

striae have often been observed on the side of the thorax opposite to the side of the main lesion. Increased movement and coughing could explain this localization but this apparently well established fact was not confirmed in twelve cases of striae thoracicae among 5,800 tubercular patients.<sup>166</sup> Szántó<sup>166</sup> in his large series always found them on the side of the pulmonary involvement.

Transverse striae crossing the spine below the level of the shoulder blades are relatively common in spondylosis deformans but are supposed to be rare in spondylitis.<sup>167</sup>

Several authors have tried to correlate the color of the hair with the formation of striae. The results are contradictory which probably means that there is no relationship. The older primipara is less apt to develop striae than the younger one. The same is claimed of the more virile type<sup>168</sup> and of the short, authentic megalosplanchnic women.<sup>99, 169</sup> The more striae a woman develops in pregnancy the more likely she is to suffer perineal lacerations but no relation to the labor pains has been established.<sup>170</sup> It is possible that a hereditary factor has influence on the development of striae. Leven<sup>171</sup> saw lumbar striae in three of nine siblings and Siemens<sup>172</sup> twice saw concordant striae in nulliparae who were identical twin sisters. In the unique case of pregnancy of one of siamese twins the nonpregnant one did not develop striae (Hübner after Siemens<sup>173</sup>). Horneck<sup>166</sup> observed the appearance of striae after the injection of adrenal cortical extract.

The elasticity of the skin in normal pregnant women is about one-third lower than normal.<sup>174</sup> This lack of elasticity is still more marked in the presence of clinical edema and albuminuria.<sup>167, 175</sup> It starts in the third month and reaches its peak at the end of pregnancy. Though edema may lower the elasticity of the skin it does not increase the tendency to formation of striae.

Edema.—A slight increase in the amount of fluid in the skin and in the subcutaneous tissue of the pregnant women must be considered normal. This is to a large extent due to the retaining influence which estrogens and progesterone exert on sodium and water metabolism.<sup>176</sup> Surgeons know that the cleavability of the tissues is increased during pregnancy. The butchers know that it is easier

<sup>166</sup>Hannauer, K. Striae distennes in the Skin of Consumptives, *Tubercle* 23: 249-252, 1921.

<sup>167</sup>Sakita, O. Endokrin bedingte Dermosen bei Lungentuberkulose, *Skd* 49: 724.

<sup>168</sup>Sakita, O. and Winkler, W. Striae distennes cutis. I. *Wien. Arch. f. inn. Med.* 29: 221-232, 1923.

<sup>169</sup>Reyher, K. Schwangerschaftsruhen und Konstitution, *Skd f. Gynäk.* 26: 1746-1754, 1926.

<sup>170</sup>Vardelli, L. Il probabile fattore endocrino nella patogenesi delle "striae cutis trophicae", *Kadoeriol. patol. esentit* 2: 281-270 1928. *Skd* 33: 518.

<sup>171</sup>Vardelli, L. Le "striae cutis trophicae" *Glor. Ital. di derm.* 67: 75-807-827 1925.

<sup>172</sup>Radevert, J. Striae gravidarum, *Arch. f. Frauenk.* 24: 180-206, 1921.

<sup>173</sup>Leven, A. *Erkrankungen der Haut*, 2. Aufl., 1922, 232-236.

<sup>174</sup>Siemens, H. W. Die Vererbung in der Ätiologie der Hautkrankheiten, *Handb. d. H. Ok.* 2: 166, 1931.

<sup>175</sup>Dario, C. Alcune ricerche di elastometria cutanea nel campo ostetrico-ginecologico, *Ri. Nat. digesta* 11: 52-54 1930. *Skd* 35: 210.

<sup>176</sup>Asselin, F. Über das Verhalten der Hautelastizität während der Schwangerschaft, *Dtsch.* 1930, *Frankf. M. Skd* 41: 202.

<sup>177</sup>Tjor, H. C. J. Warner, R. O. and Walsh, L. A. Relationship of Estrogen and Progesterone to Edema of Normal and Toxic Pregnancy. *Am. J. Obst. & Gynec.* 48: 547-568, 1943.





sign if the stases do not completely disappear on changing from the upright to the horizontal position<sup>1006</sup>. In edema and with high sedimentation rates stases are pronounced. In hydramnion a tortuous appearance of the capillary loops has been noticed.<sup>1007</sup> It should be emphasized that stases of course are not a symptom of pregnancy. They are the expression of an impaired peripheral circulation and occur in many conditions. The number of capillary loops increases in two-thirds of the pregnant women after the second month but not infrequently only as late as in the seventh or eighth month (Vinogradova after Melbard<sup>1008</sup>).

Two months after delivery the normal number of hair pin type capillary loops is usually found again.

The high permeability of the capillary wall is shown by the fact that the tourniquet test is positive in 80 per cent of the pregnant women.<sup>1007</sup> The serum of blisters produced by cantharides on the skin of pregnant women contains three to four times more lymphocytes than under normal conditions. This observation can be interpreted as evidence of the higher endothelial permeability.<sup>1007</sup> Other studies of cantharides reactions<sup>1009</sup> showed opposite conclusions.

Pregnancy is by far the most frequent cause of varicose veins in women. Only about 3 per cent of the women patients of a large varicose vein clinic had their trouble before their first pregnancy.<sup>1000</sup> The incidence figures given by a number of authors vary within wide limits but 50 per cent does not seem too high. They most often involve the lower legs only with a preference for the right side. In almost 20 per cent of the pregnant, varicosities of the vulva may produce large bluish tumorlike convolutions.

Hemorrhoids are almost as common as varicose veins of the vulva.

The most simple explanation of the varicosities of pregnancy is the pressure of the uterus on the large pelvic veins. However this cannot be the only cause since varicose veins sometimes develop in an early stage of pregnancy when pressure is negligible. They sometimes appear as an early symptom of pregnancy soon after the first missed menstruation (Balard and Mehon after Vignes<sup>1004</sup>). Even at the common time of appearance in the third month the pressure of the uterus does not give a very plausible explanation since uteri of equal size with tumor hardly cause varicose veins. Other observations<sup>1004</sup> can be interpreted against the purely mechanical pathogenesis. The varicose veins of pregnancy often appear in crops and the temperature over newly developed varicosities is up to four centigrades higher than over older ones and over the symmetrical skin.<sup>1004</sup> It is interesting that large intra-abdominal tumors may cause edema but rarely varicose veins. The elastic fibers in the wall of the varicose

<sup>1006</sup>Priller, J. Gravitätsdermatosen. *Endokrinologie* 27: 28-301, 1935.

<sup>1007</sup>Steffard, S. J. Valeur diagnostique de la capillaroscopie dans la grossesse et dans le sepsis puerpéral. *Gynäk et Gyn* 37: 200-209, 1934.

<sup>1008</sup>Alphart, R. Cantharidenreaktion und Schwangerschaft, Monatsschr. f. Geburtsh. Gynäk. 73: 47-52, 1929.

<sup>1009</sup>Petersen, W. F. and Lamb, A. F. Permeabilité des capillaires cutanés pendant la gestation. *Arch. Int. Med.* 59: 1-1, 1937.

<sup>1000</sup>St. Danhaud, A. M. Varicose Veins in Pregnancy. *West J. Surg.* 47: 1-24, 1929.

<sup>1001</sup>Schäfer, A. Varicen und Schwangerschaft. *Med. Klin.* 37: 1327, 1931.

The outbreak of the disease is often preceded by premonitory itching with out visible changes other than a few wheals. Often in this prodromal period nausea, headache and fever may be observed but lack of uniformity characterizes this phase just as much as the later stages. The rash hardly ever breaks out on large surfaces. Usually in one or a few areas e.g. around the navel and on some parts of the arms erythematous patches appear which lead to the fully developed syndrome. Wheals, prurigo-like small papules, vesicles, pustules, groups of blisters and bullae appear in crops and create a rather polymorphic picture. While at times erythematous and urticarial lesions predominate in other periods the abundant bullae may present a pemphigus-like aspect. In some cases aggregated scratched small papules on the trunk and on the extremities resemble prurigo Hebra. This dermatosis has been described as a separate dermatosis under the name of prurigo gestationis.<sup>170</sup> It is probably only a variety of the highly polymorphic herpes gestationis.<sup>171</sup> Everybody who has observed cases of dermatitis herpetiformis over a long time knows that such prurigo-like stages occur. However the separation of prurigo gestationis from herpes gestationis is still stressed by some authors.<sup>144</sup>

The erythematous and vesicular patches of herpes gestationis often spread centrifugally leaving annular or gyrate lesions with accentuated edges and red scaly or pigmented centers. There is little tendency to involve the mucosae. Ulceration does not occur and no scars develop unless severe pyogenic infection complicates the course. Besides the discomfort of large oozing surfaces in some cases the main complaint of the patients is the furious itching, burning, stinging or pain which accompanies the crops. The attacks of pruritus in particular which can be provoked by various causes especially psychic excitement can make the condition of the gravid woman a most miserable one. It needs all the efforts of dermatological and psychological treatment and in particular the assurance of complete recovery without disfigurement to keep up the morale of the patient.

The eruption affects the extremities more often than other regions but no part of the body surface is sure to remain free. The nailbeds may become infected and the nails may be shed. The outstanding histological feature is the eosinophilia in the blister serum and in the tissue particularly in perivascular infiltrations. Blood eosinophilia is common too. Eosinophilia especially in the tissue though not being specific, frequently accompanies allergic diseases and therefore suggests an allergic nature of the dermatosis.<sup>18</sup> The recession of the blood eosinophilia is considered a favorable prognostic sign.<sup>174</sup>

The relationship to pregnancy is of course an outstanding characteristic of the disease. Though occasionally an early symptom of pregnancy herpes gestationis has been seen to appear most often in the second half of pregnancy.<sup>172</sup> If there are attacks in subsequent pregnancies the onset may be earlier each time.

<sup>170</sup>Reeher J. Sur la question d prurigo, 3rd I. transl. *Cancer of Dermis*. London, 1901.

<sup>171</sup>Dirck E. Herpes gestationis, II. mth d II. Ok 7 2 837-851 1931.

<sup>172</sup>Ellensted O. Sur la valeur de l'éosinophilie dans les dermatoses bulleuses et apurieuses dans la dermatite herpétiforme de Duhring. *Naug* 21: 1-3 1925.

and the disease may become more severe.<sup>1763,1766-1767</sup> Besides this most common type other relations to gestation occur. Some pregnancies may remain free and only in a later pregnancy will the first eruption occur (Puente Gross in discussion to Rostenberg.<sup>1766</sup>) A normal pregnancy may be had between pregnancies with herpes gestationis.<sup>1769</sup> The onset may be very late, in the last days of pregnancy<sup>1768</sup> or even in the puerperium. The disease may break out during pregnancy improve or heal with the approaching delivery and then be followed by a severe crop during the puerperium.<sup>1770</sup> Characteristically herpes gestationis does not remain after pregnancy as an ordinary dermatitis herpetiformis. In a few cases menstrual recurrences have been observed.<sup>1771,1772</sup> So far unique is the case of herpes gestationis caused by choriocarcinoma two years after a pregnancy with hydatidiform mole.<sup>1773</sup>

The prognosis is favorable for the mother. A fatal outcome is rare and may be caused by sepsis rather than by the dermatosis itself (Schönfeld after Riecke.<sup>1763,1766,1774,1775</sup>)

The prognosis for the child is unfavorable. Stillbirth ends about fifty per cent of the pregnancies complicated by herpes gestationis.<sup>766</sup> Babies born alive died in several instances from infection during the first year.<sup>1766,1768</sup> Skin lesions in the living or dead child possibly pertaining to the dermatosis of the mother have been reported<sup>1766,1769,1771</sup> but the evidence of true congenital herpes gestationis is not convincing.<sup>1766</sup>

The etiology and pathogenesis of herpes gestationis is not much better understood than that of dermatitis herpetiformis. It is just the connection with pregnancy which suggests some explanation. Toxemia of pregnancy with damage to the liver to the kidneys and to the skin has often been accused. The nitrogen content of the urine is reduced during the eruption and increases with recovery. Just as in dermatitis herpetiformis, eruptions may be precipitated by internal or percutaneous application of potassium iodide (Jadassohn's test). However this phenomenon is not constant. Endocrine secretions may as in the case of impetigo herpetiformis provide a better explanation than those given today. Rostenberg<sup>766</sup> in his case found the anterior pituitary like principle increased in the urine twenty-six days after delivery. In Elliott's<sup>1771</sup> case of herpes gestationis caused by choriocarcinoma the pregnancy tests were strongly

<sup>1763</sup>Hackett, E. Ein Fall von Herpes gestationis mit tödlichem Verlauf, *Genev. Tijdschr. Nederl. Indis.* 66: 1064-1065, 1929. *Id.* 81: 87.

<sup>1764</sup>Hewari, R. Herpes Gestationis, *Arch. Dermat. & Syph.* 28: 732, 1923.

<sup>1765</sup>Madson, J. F. Herpes gestationis, *Arch. Dermat. & Syph.* 32: 450, 1924.

<sup>1766</sup>Rostenberg, A. Herpes gestationis, *Arch. Dermat. & Syph.* 30: 736, 1924.

<sup>1767</sup>Arch. E. Contributo allo studio dell herpes gestationis, *Gior. Ital. di dermat.* 47: 73, 1922-1923, 1922.

<sup>1768</sup>Worot, J. J. and Boulignot, H. Polymorphe Schwangerschaftsdermatitis, *Rev. argent. dermat.* 47: 15: 1, 1932. *Id.* 43: 478.

<sup>1769</sup>Tommasini, L. Contributo allo studio della herpes gestationis, *Gior. Ital. di dermat. ven.* 66: 840-842, 1922.

<sup>1770</sup>Cruick, A. Herpes gestationis dermatitis pellucida delorago (Dühring-Brace), *Gior. Ital. di dermat.* 47: 73: 163-174, 1932. *Id.* 43: 83.

<sup>1771</sup>Elliott, J. A. Sebaceous Dermatoses of Toxic Origin. Case Involving an Association With Choriocarcinoma, *Arch. Dermat. & Syph.* 87: 219-223, 1923.

<sup>1772</sup>Mabeffon, W. Ein Fall von Herpes gestationis, *Jap. J. Dermat. & Urol.* 23: 43, 1923. *Id.* 48: 201.

<sup>1773</sup>Orlborn, E. Eczema in Pregnancy, *Am. J. Obst. & Gynec.* 28: 409, 1932.

positive. The relationship of dermatitis herpetiformis to ovarian function however inconstant and contradictory it may be cannot be easily dismissed in view of the considerable case literature.<sup>1 2</sup> However there still is no satisfactory endocrine explanation. Some evidence points to allergy. The repeated occurrence in pregnancies with each subsequent attack starting earlier and taking a more severe course has its parallel in acquired allergy. The urticarial element in the eruption and the marked eosinophilia in the blood blisters and tumours lend support to an allergic hypothesis. Passive transfer has not been successful.<sup>173</sup> A hormone may well act as an allergen. Tommasi<sup>171</sup> suggests the corpus luteum such autogenous allergies are known. Infection as a cause can neither be denied nor as yet be proved. Thus the pathogenesis of herpes gestationis as well as that of dermatitis herpetiformis remains unknown.

Based on the hypothesis that herpes gestationis is caused by toxemia and the inability to produce neutralizing antibodies Mayer and Linser<sup>174</sup> inaugurated the treatment of herpes gestationis with intravenous injections of 10 to 20 c.c. of fresh serum of normal pregnant women. With this method Seitz cured 37 out of 38 cases of the various dermatoses of pregnancy. This method is still widely applied. In some countries this serum is available in ampoules. The serum of pregnant mares has been successfully used too. In spite of successes the theoretical foundation of the treatment with normal pregnant women's serum however has become untenable because of the equally successful treatment with normal serum horse serum and especially with Ringer's solution. Recke<sup>175</sup> gives the following formula for this mixture:

Sodium chloride	18
Calcium chloride	0.018
Potassium chloride	0.084
Sodium bicarbonat	0.06
Aq. destill. ad	200 ml

This solution is injected intramuscularly or subcutaneously in doses of 150 to 200 c.c. Similar success has been achieved with serum or blood from the umbilical cord with the patient's own blood<sup>71</sup> and with milk. In the published cases one or the other of the above mentioned methods especially the normal pregnant women's serum has helped. One may surely assume however that failures of the therapy have not been reported with the same zeal as the successes. Only a few of the observers have seen a considerable number of cases of this rare disease and the often irregular course. If the dermatosis should be remembered in evaluating any method of treatment. Lately contradictory reports on the sulfonamides have appeared. Ovarian extract<sup>72</sup> corpus luteum<sup>73</sup> and vitamin D<sup>74</sup> have also been administered.

<sup>1</sup> L. J. A. and Linser: Ein Versuch Schwangerschaftstoxikosen durch Einspritzen von Schwangerschaftsserum zu heilen. *Matern. und Wehnenh.* 37: 2737-2749 1910.

<sup>2</sup> Warrin, J.: Dérivés polymorphes conjugués et atropho-ecthymateux. *Bull. Soc. franç. de dermat. et syph.* 31: 1424.

<sup>71</sup> Turner, J. and Zakon, J.: Herpes Gestationis. *Am. J. Obst. & Gynec.* 41: 825-837 1941.

<sup>72</sup> Leach, M.: Herpes Gestationis: Successful Treatment With Palfishian's, *Arch. Dermat. & Syph.* 48: 1: 1942.

**Purpura**—It has already been mentioned that pregnancy increases the permeability of the capillary wall and that the tourniquet test (Rumpel Leede phenomenon) is often positive. Spontaneous petechiae are occasionally seen under the strain of labor. More severe purpuric rashes have been observed<sup>72</sup> some of them with dangerous hemorrhagic complications. They are generally considered toxic. They disappear after delivery<sup>122</sup> but sometimes recur in subsequent pregnancies, in some cases in the same spot as a fixed eruption<sup>123</sup> Rushmore<sup>122</sup> has collected forty-seven cases, mostly of severe purpura in pregnancy. The mortality of the mothers as well as of the children exceeded fifty per cent. Some cases have the character of thrombocytopenic purpura.<sup>72</sup> Pregnancy may activate dormant thrombocytopenic purpura or cause the first manifestations of the disease. Besides purpuric skin lesions of great variety in size severe even fatal hemorrhages from the nose, the gums and other sites may occur. If treatment fails, termination of the pregnancy is indicated. Bruise like hemorrhagic discolorations of the abdominal wall in and about the umbilicus occur in ruptured extrauterine pregnancy and other intra-abdominal hemorrhages. This is known as Cullen's sign.<sup>72</sup>

**Miscellaneous Eruptions**—It would be monotonous to describe all the rashes which have been observed in pregnancy other than the well characterized dermatoses. There are morbilliform erythemas, sometimes with eczema or with pruriginous papules. Erythema exudativum multiforme<sup>124,125</sup> is also on record. Its differentiation from herpes gestationis is difficult in some cases. Urticaria of pregnancy angioneurotic edema and lichen urticatus are known. Pruritus of pregnancy is common and sometimes of a severity which may cause abortion.<sup>144</sup> Eczema<sup>145</sup> lichenoid multiple lesions resembling localized prurigo<sup>77</sup> pemphigus vulgaris,<sup>127</sup> scleroderma<sup>172,173</sup> cutaneous atrophy in spots (Temesvary and Oppenheim after Novak<sup>143</sup>) and other conditions have occasionally been seen during pregnancy sometimes repeatedly and usually healing after delivery. Selitzky<sup>144</sup> described toxic symmetrical dermatitis. It has been said that the pregnant woman has a marked tendency to develop drug eruptions.<sup>172</sup> Pruritus vulvae and vulvitis of pregnancy is often caused by monilia but is rare compared with

<sup>72</sup>Kahn K. *Seitene Hautveränderungen bei Schwangeren*, Med. Klin. 24 822-824, 1923.

<sup>122</sup>Vigors, H. and Stimson. *Purpura additivat au cours de trois gestations successives*, Progrès méd. 69: 167-168, 1921. *Ibid.* 1 445.

<sup>123</sup>Rushmore, S. *Purpura Complicating Pregnancy* Am. J. Obst. & Gynec. 19 323-330, 1925.

<sup>124</sup>Selitzky J. *Pregnancy Complications—Thrombocytopenic Purpura*, *Stecher f. Geburtsh.*

*Gynäk.* 119 65-68, 1923.

<sup>125</sup>Cutler, T. B. *Bluish Umbilical as Diagnostic Sign in Ruptured Extrauterine Pregnancy* Contributions to Medical and Biological Research, etc., New York, 1919 Paul H. Hoeber pp. 430-431.

<sup>127</sup>Green, P. *Erythema multiforme gestationis*, Arch. Dermat. & Syph. 22: 567 1921.

<sup>172</sup>Elbert. *Toxic Eruption of Pregnancy Multiform Erythema Type*, Arch. Dermat. & Syph. 21: 508-510, 1927.

<sup>144</sup>De Lee, J. H. T. *Prurigo Annularis*, Brit. J. Dermat. 53: 142-143, 1941.

<sup>145</sup>Kloppstock. *Pemphigus vulgaris Associated With Pregnancy* Dermat. Wochs. 69: 304, 1924.

<sup>173</sup>Amannstein K. J. and Hoffman, F. *Ueber Scleroderma und Schwangerschaft*, *Stecher f. Geburtsh. Gynäk.* 192: 60-66, 1922.

<sup>174</sup>Gerard. *Cas de scleroderme au bras et à la suite d'une grossesse* *Troubles variés*, Le scalpel 2: 314, 1929. *Ibid.* 22: 78.

<sup>143</sup>Novak E. *Skin During Pregnancy and Puerperium*, *Int. & Cutan. Rev.* 48 80-82, 1944.

the frequent occurrence of yeasts in the vagina of pregnant women.<sup>172</sup> The typical monilia vulvitis causes itching and redness of the introitus and of the vagina. Yellow specks of thrush which are not easily removed without bleeding contain the mycelia. Vaginal thrush caused by *Monilia albicans* was found in 25 per cent of 200 consecutive pregnancies having leukorrhea in Edinburgh Scotland.<sup>173</sup> It is advisable to look for vaginal thrush in order to safeguard the baby from infection at birth. Very little is known about the cause of the more severe ulcerations of the external genitalia in pregnancy which have occasionally been seen.

**Stimulation of Growth**—Symmetrical erythema of the palms mainly on the thenar, hypothenar and finger tip eminences has been described in connection with a variety of internal conditions, notable among them being cirrhosis of the liver and pregnancy. The erythema usually leaves the triangle-shaped center of the palms pale. The condition is often associated with multiple sometimes pulsating spider like telangiectases.<sup>174-176</sup> The erythema as well as the telangiectases often vanishes after parturition. In some cases the spiders result in actual hemangio-endotheliomas which may even become locally malignant and infiltrating.<sup>177</sup>

Preexisting and apparently stationary hemangiomas may start to grow during pregnancy.<sup>178</sup>

Fibroma molluscum gravidarum<sup>729-734</sup> is an eruption of small soft pedunculated or sessile sometimes pigmented firmmas which appears in crops during the latter half of pregnancy and disappear after childbirth. The little growths appear especially around the neck and in other areas where skin rubs against skin e.g. under pendulous breasts and in the axillary folds. They may be associated with large brown spots so that a close resemblance with Von Recklinghausen's disease results including the microscopic anatomy. The lesions which appear during pregnancy usually<sup>73</sup> but not always<sup>72</sup> disappear after delivery. While the widespread or even universal types of fibromatosis gravidarum as it should be called<sup>72</sup> are rare a crop of some cutaneous tags<sup>734</sup> around the neck is common in pregnancy. Pregnancy stimulates the growth of skin cancer

<sup>172</sup>W. C. K. G. and Carter R. E. W. Maintenance of Vulvovaginitis in Pregnancy. *J. A. I. A.* 113: 30-31, 1939.

<sup>173</sup>Larson W. C. and Crankshaw L. G. On Thrush. Special Reference to Vaginal Thrush. *Edinburgh J. J.* 67: 260-1, 10.

<sup>174</sup>Hoernel E. Erythematöse Triangulärektasen bei Cirrhose. *Zbl. Bt.* 57: 274, 1925.

<sup>175</sup>Wald E. V. and Berke W. Erythema palmaris und Vena Arterialis Triangulärektasen. *Arch. Derm.* 4: 181-182, 1911.

<sup>176</sup>Lythark E. Erythematöse Triangulärektasen. *Zbl. Bt.* 58: 329, 1926.

<sup>177</sup>De H. J. M. Benignes Hemangioendotheliomas in Pregnancy. *J. Obst. & Gynec. Brit. Emp.* 45: 607-673, 1938.

<sup>178</sup>Lythark E. Abhängigkeit eines Angioma von einem von Schwangerschaft und Menstruation. *Zbl. Bt.* 58: 1, 1926.

<sup>729</sup>Drickner M. Fibroma Molluscum Gravidarum. *Am. J. Obst. & Gynec.* 52: 181, 1904.

<sup>730</sup>Drickner M. Molluscum Fibrosum Gravidarum. *Am. J. Derm.* & Gyneco-Obst. 18: 181, 1904.

<sup>731</sup>Drickner M. Über das Fibroma molluscum gravidarum. *Zbl. f. Gynäk.* 61: 727-729, 1909.

<sup>732</sup>Ward F. Multiple Papules of Warts in Pregnancy. *Brit. J. Derm.* 25: 143, 1913.

<sup>733</sup>Ward F. Über den Einfluss der Schwangerschaft auf das Entstehen und Wachsen von Warzen. *Arch. Derm. & Syph.* 52: 615-64, 1903.

<sup>734</sup>Thompson H. J. Cutaneous Tags of the Neck. *Arch. Derm. & Syph.* 52: 95, 1934.

produced in rabbits by the application of carcinogenic tar fractions.<sup>170</sup> The growth stimulating effect of the estrogens is suggested as a cause. The hypercholesteremia of pregnancy makes one expect a rather frequent occurrence of

Fig. 216.



Fig. 217

Fig. 216.—Fibroma of pregnancy

Fig. 217. Fibromas (cystic type) of pregnancy. These little tumors can appear early in pregnancy and some may reach larger size.

lipoidoses. It is surprising that xanthoma and xanthelasma in connection with pregnancy is rare (author's case see also Schaaf<sup>171</sup>). Growth stimulation may also be the cause of the so-called gingivitis hypertrophica of pregnancy. This

<sup>170</sup>Kretschka, M. Über den Einfluss von Gravidität und Lactation auf die durch Trepanwachstum erzeugten Epithelwucherungen am Kanarienvogel. *Zeitschr. f. Krebsforsch.* 23: 458-482, 1921.



disorder<sup>1746,1747</sup> frequently starts in the third month. In the early stages the gums are red and bleed easily. Then they swell especially at the margin. The bulging edge may develop folds which cover the teeth and cause considerable trouble. If this hypertrophic stage is restricted to a small area an epulis-like nodule may result. The term epulis gravidarum which has been used is misleading because of the different character of the two conditions. However true epulis occasionally starts in pregnancy and the growth of a preexisting epulis (Seitz) or giant cell sarcoma<sup>1747</sup> may be stimulated. The swelling of the gums disappears quickly after delivery sometimes within a week. Gingivitis hypertrophica of some degree is seen in more than half of all pregnant women. In 32 per cent the condition was moderately severe and in 4 per cent severe.<sup>17</sup> These figures were observed in Germany and may well differ from those of other countries.



Fig. 218.—X. Ithelness, started in pregnancy

This gingivitis of pregnancy is primarily a connective tissue hypertrophy. The inflammation seems to be secondary although it may dominate in the fully developed case. It has been shown that similar hypertrophy of the gums can be produced in monkeys by injection of the concentrated urine of pregnant women.<sup>749</sup> Huber<sup>1750</sup> found a high level (700 M U) of follicular hormone in one liter of urine of a twelve-year-old boy who suffered from hypertrophy of the gums. Newborn children often show a comparable succulence of the oral mucosa which disappears within a few days leaving the empty suckling folds. This may be one of the effects of the maternal or placental hormones. Vitamin C deficiency and hypocalcemia are accused by other mostly European dentists of being the main cause of gingivitis in pregnancy. The proponents of this theory base their opinion on the low content of vitamin C in the serum of pregnant

<sup>1746</sup>Fortier, J. Gingivitis in Pregnancy. *Union med. du Canada* 68: 845-846, 1936.

<sup>1747</sup>Mossab, B. Proliferative Gingivitis of Pregnancy. *Cases, Arch. Dermat. & Syph.* 31: 340-346, 1931.

<sup>1748</sup>Krebeck, J. Schwangerschaftsgingivitis. ad ihre Behandlung mit Kalk und Vitamin C. *Arch. f. Gynäk.* 169: 571-576, 1929.

<sup>1749</sup>Blackie, H. Blackie, G. and Stout, A. F. The Gingivae During Pregnancy. *Burg. Gynec. & Obst.* 67: 719-736, 1933.

<sup>1750</sup>Huber, H. Zahnfleischkrankungen in der Schwangerschaft. *Zbl. f. Gynäk.* 82: 1977-1991, 1939.

women suffering from gingivitis compared with normal controls, and on the therapeutic effect of vitamin C.

Many dentists advise treatment with Vitamin C and calcium. It is claimed to be helpful if the process is not too far advanced.<sup>1719,1720</sup> The teeth should be cleaned, checked and treated at the beginning of pregnancy in order to minimize secondary infection. Only complications require local treatment.

The treatment of the dermatoses of pregnancy is both topic and systemic. The former is determined by the type and stage of the lesion. In the vast majority



FIG. 21. Severe skin eruption in pregnancy. There is almost no scar present before

of the cases, it is possible to keep the patient comfortable or to heal the eruption even during pregnancy. In the more severe and of course the dangerous cases the treatment should follow the methods described under herpes gestationis. Ringer's solution should always be tried first since it is not connected with any risk. Its antipruritic effect has been praised.<sup>1721</sup> Injection of 1 to 5 c.c. of the

<sup>1719</sup> Brauer R. Pregnancy Complications, Gingivitis, Med. Klin. 28: 290-291, 1929.

<sup>1720</sup> Sahn, S. L. and de Castro-Lanes, S. P. Treat. ment of Pruritus of Pregnancy With Ringer Solution, Semana Méd. 2: 161-162, 1937. *Id.* 5: 642, 1939.

patient's own blood has also been recommended.<sup>178</sup> The serum of normal pregnant women should be given if Ringer's solution fails. In these cases the question of the artificial termination of the pregnancy will arise. In herpes gestationis the prognosis is favorable for the mother and less so for the child. These cases will rarely require the termination of the pregnancy. If the diagnosis of impetigo herpetiformis is made the pregnancy should be interrupted as soon as possible before large areas become involved and infected and make the operation dangerous. Even early abortion does not secure an absolutely favorable prognosis.<sup>179</sup>

**Influence of Pregnancy on Existing Dermatoses**—Pregnancy often influences the course of existing dermatoses. The observations regarding *psoriasis* are contradictory but improvement during pregnancy occurs quite often. The same is said of *acne* (Kaufmann in discussion to Seitz<sup>180</sup>) but here too the observations are conflicting.<sup>181</sup> The author has seen at least two cases of *acne conglobata* with severe exacerbations during pregnancy.

In several strikingly parallel instances patients with *alopecia areata totalis* regained their hair during pregnancy only to lose it again a short time later. Seborrheic alopecia usually improves or is arrested.

Some contrasting observations on scleroderma and pregnancy have appeared (Jadassohn in Wiener<sup>182</sup>, Jell<sup>183</sup>, Jell<sup>184</sup>). (See scleroderma.)

Von Recklinghausen's disease often takes a turn for the worse in pregnant women.<sup>185</sup>

<sup>178</sup>Lyander A. Behandlung der Schwangerschafts-Dermatosen, Svenska Läk.-Tidning 31: 23-29 1934. Ed. 49: 151.

<sup>179</sup>Barpe, J. G. and Young, R. H. Neurofibromatosis. Effect of Pregnancy on the Skin Manifestations. J.A.M.A. 104: 682-683 1936.

## CHAPTER XXIV

# CHILDBIRTH AND PUERPERIUM THE SKIN IN THE NEWBORN

### Childbirth and Puerperium

**Emphysema.**—In rare instances the intrathoracic pressure caused by the labor pains can puncture the lung tissue and press the air under the visceral pleura along the mediastinal spaces to the neck. Once such an air channel is formed more and more air is pumped into the loose connective tissue. Finally the subcutaneous tissue becomes inflated and painful and gives the palpating finger the crepitant sensation found in some chest injuries and in gas gangrene. The first symptoms of subcutaneous emphysema are most frequently found in the face, less often in the nape of the neck or above the sternum.<sup>766</sup> Some authors feel that the phenomenon is better explained by rupture of the tracheal wall due to the intense vibration caused by screaming. Pleural adhesions are also believed to play a part.<sup>766,776</sup> Only very rarely has an actual laceration of lung tissue been verified at autopsy (Depaul after Scheuer<sup>1893</sup>). Even laceration of the buccal mucosa with ensuing emphysema has been observed.<sup>1766,1776</sup> The clinical picture of the frog-like inflated neck, from where the emphysema may travel long distances under the skin must be impressive but even very experienced obstetricians have encountered it extremely seldom about once in several thousand confinements. The patients were almost exclusively primiparae with pelvic contraction and very large babies. The prognosis of the emphysema per se is usually favorable.

**Petechiae.**—Since pregnancy creates a purpuric tendency it is not surprising that under the strain of labor petechiae appear. They are most often seen in the conjunctivae and on the neck and shoulders rarely over the entire body.<sup>827,774</sup>

**Urticaria.**—Urticaria beginning with labor and disappearing two days later has been seen.

**Pruritus**<sup>770</sup> and *Herpes* occur occasionally in the first day of the puerperium

J Jadassohn, personal communication also author's notes

<sup>774</sup>Kormak, G. W. Cutaneous Emphysema During Labor. Bull. New York Lying-In Hospital 1907 Abstr. *Int. J. Gynec.* 82: 1029-304.

<sup>776</sup>Priedefer, H. Cervicothoracic Subcutaneous Emphysema. *Ann. Rev. de gynec. Obstet.* 2: 183-183 1913

<sup>776</sup>Garret, W. *Traité de Obst.* ed. 2, Vol. I p. 207 1932

<sup>1766</sup>Weyburn, J. D. and Martin, H. E. Trauma to Purpura Occurring During Labor. *J. Obst. & Gynec. Brit. Emp.* 66: 303-304 1923

<sup>1776</sup>Klimewich, W. A. Postnatal Complaints in 1000 Consecutive Cases. *Illinois M. J.* 74: 436-441 1924

**Nail Hair**—Not all the dermadromes of labor become immediately apparent. The great event leaves its mark on the growing tissues of the nails and hair but it is only considerably later that these sequelae become evident. From twenty-one to forty two days after the delivery transverse grooves or lines, very rarely only white stripes may appear on the proximal ends of all fingernails or on some symmetric nails. These lines which are known as *Beau's lines* are more pronounced on the nail of the thumbs and the first fingers than on the smaller



Fig. 220



Fig. 221

Fig. 220 —Hoof of an old cow showing periodical line formation. (Courtesy University of Wisconsin, Department of Dairy Husbandry)

Fig. 221 —Horn of an old cow. Physiological ring formation in regular intervals except on the free end which represents the oldest part of the horn formed during the first years of life. The rings become less distinct the older they are. (Courtesy University of Wisconsin, Department of Dairy Husbandry)

fingers. They are not always present but they are quite common. They may occur after any acute disease and after gastrointestinal, cardiac and other attacks. Therefore they alone cannot be regarded as a certain indication of preceding childbirth. Since it takes about thirty days for the nail to appear under the edge of the cuticle and since the nail grows about 0.1 mm a day, it seems easy to calculate retrospectively the day of delivery. But individual differences in the rate of growth and other factors make a more accurate determination than the week of the event impossible.<sup>441</sup>

*Beau's lines* also appear on the nails of the newborn (see newborn). Comparable to *Beau's lines* of the human nails, ring formation on the horns of cows

after calving are commonly observed and used as an indication of age. Similar marks are known to occur on the hooves of mares.

The growing hair is affected by the trauma of childbirth just as is the nail. A considerable number of hairs are so weakened that they fall out after two to three months. Other hairs show only a thinned portion of varying length (Pohl-Pinkus mark). If the puerperium is complicated by fever and infection the mark may involve a longer stretch. This mark is not only thinner but also lighter in color. Considering the daily rate of the head hair growth as 0.3 — 0.5 millimeter or approximately 1 cm. per month<sup>142</sup> it is possible to determine the day of the delivery within certain limits. If several pregnancies follow each other closely the hair does not have enough time to recover and stays thin and short. Some veterinarians believe that animals who are prevented from eating the placenta lose much hair<sup>144</sup> even to the degree of complete epilation. Gross advises administration of 5 gm. of placental extract three times daily for the treatment of post partum hair loss in women. His series of 24 patients, afflicted with a condition which offers a good prognosis anyway needs confirmation on a larger scale.

Skin irritations from the lochia and dermatitis around the nipples, shall be mentioned for the sake of completeness. Simunich noted in one thousand consecutive cases, the following postnatal complaints concerning the skin: five cases complained of pruritus, four of which involved the extremities only one the vulva. There were four cases of excessive perspiration and four cases of herpes between the second and seventh days. In seven cases the axillary glands were swollen. Reports of infections of many kinds,<sup>143</sup> and onset of chronic diseases, are numerous, but no characteristic dermatoses seem to have been described in relation to this phase. Puerperal sepsis may exhibit itself in erythematous, morbilliform scarlatiniform and other rashes. Exfoliative dermatitis probably caused by *Staphylococcus aureus hemolyticus* has been seen.<sup>145</sup> Purpura occurred also in the course of puerperal complications. Sensitization of a woman to her own milk, with allergic symptoms like urticaria and angioneurotic edema is considered possible though still lacking confirmation.<sup>144</sup>

The dermatoses of pregnancy usually subside in the postnatal period but exacerbations in the early puerperium are especially characteristic of herpes gestationis.

<sup>142</sup>There are two types of ring formation on the horns of cattle. Normally rings appear at the base of the horns in both sexes every year after the third year. It seems that they are caused by seasonal change of food. Besides this physiological ring formation, any event which depresses the metabolism of an animal deep enough may leave its mark on the growing horns. Such events may include disease, nutritional changes, and also pathological births. The normal births do not seem to cause rings. Analogous phenomena are important in the hair of sheep. Subcutaneous nutrition causes thickening of the hair even to such an extent that the hair breaks off and the fleece may become lost. (Personal communication from Prof. E. Heider, Department of Dairy Husbandry, University of Wisconsin.) (See also J. Heider<sup>1922</sup>)

<sup>143</sup>Heider, J. *Tierdermatosen*, Handb. d. H. u. Gk. 14, 1: 719-917, 1930.

<sup>144</sup>Gross, E. R. *Dermatology in Relation to Endocrinology*, Chicago 8: 812-822, 1914.

<sup>145</sup>De Lee, J. B. *The Principles and Practice of Obstetrics*, ed. F. Philadelphia and London 1929, W. B. Saunders Co.

<sup>146</sup>Heider, A. *Exfoliative Dermatitis Due to Staphylococcus Aureus Hemolyticus During Puerperium*, *Abh. f. Geburtsh. Gynäk.* 89: 271-272, 1930.

<sup>147</sup>Duke, W. W. *Allergy, Asthma, Hay Fever, Urticaria and Allied Manifestations of Reaction*, 8: Lewis 1925, The C. V. Mosby Co.

Poecoriasis which quite often disappears in pregnancy commonly recurs during lactation

### The Skin in the Newborn

The skin of the normal and fully developed newborn baby is red (erythema neonatorum physiologicum) and covered with vernix caseosa. The fetal lanugo hair has disappeared with the exception of some fuzz on the shoulders and on the back. The head is usually covered with hair of up to one inch (2.5 cm) in length. The eyebrows and eyelashes are developed. The nails have a palpable horny consistency and slightly exceed the fingertips in length. The panniculus adiposus is well developed and causes characteristic bulges and folds especially on the buttocks and thighs.

Microscopically the horny layer of the epidermis is very thin<sup>70</sup> and the nuclei stain well throughout the epidermis.<sup>70-177</sup> The papillae are flat but the papillary vessels are hyperemic. The tunica elastica of the blood vessels is well developed in contrast to the media and adventitia.<sup>70</sup> The other elastic fibers are still but little differentiated.<sup>70</sup> It takes about three years until the elastic reticulum is developed approximately like that of the adult. The corium is rich in cells. The fat cells have in contrast to the adult well-discernible nuclei. The Pacinian corpuscles are completely differentiated. In spite of the developed musculi arrectores pilorum goose flesh does not occur in the newborn.<sup>176</sup> The hairs are devoid of a medulla.

The sebaceous as well as the sweat glands assume their characteristic shape and full function after the fourth or fifth month<sup>70</sup> of extrauterine life but secretion is present<sup>70</sup> as early as the sixth month of embryonal life. Milla neonatorum are either enlarged sebaceous glands or cysts filled with desquamated horn cells.

The insensible perspiration is greater<sup>178</sup> and the acidity of the newborn's skin is lower than in the adult. The average pH of 6.7 is close to the neutral point.<sup>77</sup> Of course the transition from fetal to extra uterine life affects the whole system so profoundly that it is not surprising that it is recorded in the growing matrix of the nails. Schick<sup>177</sup> determined the rate with which the physiological nail line of the newborn moves toward the free end of the nail. On the

30- 39th day the line has grown out 0.5 millimeter
40- 49th day the line has grown out 1.4 millimeter
50- 59th day the line has grown out 2.3 millimeter
60- 69th day the line has grown out 3.0 millimeter
70- 79th day the line has grown out 3.3 millimeter
80- 89th day the line has grown out 3.6 millimeter
90-100th day the line has grown out 4.2 millimeter

<sup>70</sup>Günzleben, V. F. Die Besonderheiten des Kindesalters, Berlin, 1921 Ad. Med. Verlaganstalt  
<sup>71</sup>Tausch, M. Die anatomischen Eltern Ähnlichkeiten der Neugeborenenhaut und ihre damit verbundene Disposition zu Erkrankungen, Arch. f. Gynäk. 100 378-391, 1927

<sup>72</sup>Chiale, G. De De modificazioni del vasi cutanei neonati all'età (Riv. Ital. di dermat. inf. 28 1625-1642, 1927

<sup>73</sup>Meckler, Kasal D. Elternähnlichkeiten der Haut von Kindern, Dermat. Monat. 79 684-671, 1931; Zbl. 49 443

<sup>74</sup>Hirsch, H. Die Reiz-Ischämie der Haut beim Kinde. Med. Klin. 32: 744-760 1936

<sup>75</sup>Taddel, A. Ricerche mediante indicatori sulla reazione attuale della cute nei neonati. Riv. Ital. Ginec. 18 491-519 1933.

<sup>76</sup>Schick, D. Die physiologische Nagellinie des Säuglings, Jahrb. f. Kinderh. 87 148-160, 1909.

These figures were obtained from 250 measurements. Heller is skeptical about the practical value of these measurements since individual variations are common.

On the borderline of physiological and pathological peculiarities are the milia of the face, the symphysis praeputialis which disappears by desquamation the mongol spots and the superficial epithelial cysts in the midline of the hard palate.<sup>177</sup> Several types of flat and faintly red telangiectases are known as nevi pallidi (stork bites). Unna's nevus is a relatively inconspicuous, macular purplish irregularly contoured telangiectasis of the nape of the neck. Other similar vascular maculae occur on the forehead<sup>178</sup> on the eyelids and elsewhere. Most of these vascular nevi disappear spontaneously. They should not be confused with true hemangiomas. Icterus neonatorum of varying degree occurs in about two out of three babies and clears up during the first week. A peculiarity of the infantile skin is its tendency to form blisters. Thus scabies in early childhood syphilis and even psoriasis may produce large blebs and the urticaria of this age often shows a central vesicle and a papular appearance giving it the characteristics of strophulus. The allergic skin reactions are likely to be vigorous or even violent so that a mild test reaction e. g. a moderately positive Pirquet should be judged with great caution.<sup>179</sup> Of great importance is the hemorrhagic tendency in the newborn. In 66 per cent of the babies the endothelial permeability as measured by the number of petechiae elicited under controlled conditions by the application of a suction cup is increased above the adult level. At the age of ten years this physiological hemorrhagic tendency has disappeared.<sup>178</sup>

The incidence of the more severe *hemorrhagic diathesis of the newborn* is about one in two hundred<sup>178</sup> with a marked predisposition by asphyxia at birth. The disease is not noticeable at birth. On the third day symptoms of hemorrhagic disease such as the oozing of blood from the navel from circumcision and from other wounds or bruises may become manifest. There are often large purpuric spots but, according to Quick<sup>180</sup> petechiae are characteristically absent. Melena neonatorum is the most common type of the disease. This trouble is due to hypoprothrombinemia. The prothrombin level at birth is near the adult level but it may fall during the first few days to as low as 10 per cent. It returns to normal at the end of the first week.<sup>180</sup> The cause of this drop is a deficiency in vitamin K. The human body is unable to synthesize vitamin K which comes entirely from plants. The newborn is physiologically provided with enough vitamin K from the mother to tide him over the first week, until he can draw from the harvest of his intestinal flora which becomes established during this time. If the baby does not get enough maternal vitamin K or if his allotment is used up or destroyed before his own is ready for use the level falls below

<sup>177</sup>Mayerhofer E. Hauterscheinungen der Neugeborenen. *Liefern.* vjes 88 403-407 1933 Ibl 44 743

<sup>178</sup>Lagenbeck H. Ueber Telangiectasien bei Neugeborenen. *Monat f. Geburtsh. u. Gynäk.* 89: 87 123, 1923

<sup>179</sup>Hayr W. Beitrag zu den hämorrhagischen Erkrankungen des Neugeborenen. *Die Rolle der Endothelzellen.* *Jahrb f. Kinderh* 183: 323-329, 1931

<sup>180</sup>Quick R. L. Hemorrhagic Disease of the Newborn. 354 *Casr.* *J. Pediat* 10 1 1941



the critical point and causes hypoprothrombinemia and hemorrhage. Vitamin K restores the bleeding mechanism to normal. If 2 mg. of vitamin K (menadione) are given to the mother within two days before delivery the baby's vitamin K ration is increased enough to prevent hemorrhagic disease.<sup>177a</sup> The modern treatment of hemorrhagic disease of the newborn has reduced the mortality from 57 per cent to 20 per cent.<sup>177b</sup>

A group of phenomena in the skin of the newborn is explained by the effect of maternal or placental hormones. The squamous epithelium of the vagina of newborn girls develops a marked hyperplasia and becomes piled up to a thickness of 30-40 layers with the top layer constantly desquamating.<sup>177c 177d</sup> The vaginal smear shows an abundance of naviculated squamous cells with pyknotic nuclei indistinguishable from the smear of pregnant women. This phenomenon is clinically noticeable as a creamy white discharge rarely mixed with blood from the cervix. A few days after birth regression of the hyperplastic epithelium sets in and the normal infantile vaginal mucosa develops. This phenomenon is so regularly found and so striking that it has been suggested to make use of it for the objective determination of the age of a newborn baby.<sup>177e</sup>

Not as constant as the reaction of the vaginal epithelium but well known for ages is the swelling and secretion of the mammary glands in the newborn of both sexes (witch milk). The *linea alba* especially between the navel and mons veneris becomes pigmented in 8 per cent of the babies.<sup>178</sup> This pigmentation becomes visible at the age of three weeks and persists two to three months. The succulence and sometimes even the swelling and fold formation of the gums in newborns (suckling folds) has been compared to the hypertrophic gingivitis of pregnant women<sup>179</sup> (see pregnancy). The *labia majora* and also the male genitals of the newborn are often swollen and succulent. This also may be due to hormonal influence. Other influences of pregnancy have been observed in the internal genitals of male and female newborns.<sup>179</sup>

The comedones and the false milia i. e. the enlarged sebaceous glands and the sometimes observed acne of the newborn (also has vigorous lanugo growth) have often been interpreted as hormonal pregnancy reaction. One has even in view of the numerous gonadal stimulations spoken of a miniature puberty of the newborn. The hypertrichosis of the newborn has also been called a parallel to the hypertrichosis of pregnancy.<sup>180 179b</sup>

<sup>177a</sup>Dett H. K. The Fat-Soluble Vitamins. Handbook of Nutrition Chicago 1943, American Medical Association.

<sup>177b</sup>Franeckel L. and Papadimitriou O. V. Growth, Desquamation and Involution of the Vaginal Epithelium of Females and Children With Consideration of the Role of Hormonal Factors, Am. J. Anat. 82: 477 1971

<sup>177c</sup>Philipp E. Nachweis von Schweißdrüsenveränderungen beim Neugeborenen. Klin. Wochenschr. 17 787 800, 1939

<sup>177d</sup>Grassmann H. Histologische und experimentelle Untersuchungen zur Frage des Schwangerschaftsreaktions der Neugeborenenorgane. Zentralbl. f. Geburtsh. Gynäk. 99 100-126 1970

<sup>177e</sup>Grassmann H. O. Schwangerschaftsreaktionen im Neugeborenenorganismus. Sitzungsber. d. Gesellsch. Befrucht. u. Schw. zu Marburg 85 61 120 1931

<sup>178</sup>Epstein, B. Über ein neues Zeichen der fetalen Schwangerschaftsreaktion. Acta paediat. 18 100-106, 114-121 1937

<sup>179</sup>Leiser C. Hautkrankheiten im Säuglingsalter. Handb. d. H. 22 28 3 490-537 1930

## CHAPTER XXV

### MENOPAUSE

The known physiological changes connected with the menopause are manifold. The irregularity and the final ceasing of menstruation is due to ovarian changes which may precede the actual menopause for a considerable time. Failure of the formation of corpora lutea and simultaneous persistence of Graafian follicles is thought to be responsible for a temporary oversupply of estrin which may account for menopausal hemorrhage.<sup>1763</sup> The waning function of the ovaries is followed by excessive and persistent oversecretion and excretion of the lutealizing and follicle stimulating factors of the prepituitary.<sup>1764</sup> This amount of anterior pituitary hormone which exceeds that in pregnancy by a wide margin disappears only slowly.<sup>1765</sup> Injection of large doses of estrogen makes the gonadotropic factor temporarily disappear from blood and urine. In more than 50 per cent of the menopausal women as well as in castrates considerable quantities of the estrogenic factor circulate in the blood and are excreted in the urine.<sup>1764</sup> Along with the hormonal changes appear a great number of symptoms: nervousness, exhaustion, headache, insomnia, depression, arthralgia, cardiac consciousness and obesity.

**Dermadromes—Hot Flashes and Perspiration: Formication**—In the skin hot flashes and excessive perspiration are the most common physiological phenomena of the change of life. In evaluations of large series of the menopausal syndrome<sup>1766 1767 1768</sup> the incidence of hot flashes varies from 59 to 95 per cent. This is understandable since the phenomenon is extremely variable in severity. In the typical fully developed spell the patient, often after an abdominal aura, suddenly suffers from a sensation of heat which is described as creeping from the lower parts of the body to the head. The face is usually flushed. In severe attacks the patient has the urge to open her dress and seek an open window in order to satisfy the sensation of air hunger. After a short period of about twenty seconds to three minutes the attack ends with a profuse perspiration which often causes chills. Fortunately such severe seizures are relatively infrequent and the vast majority of women experience only milder flashes. The number of attacks varies from a dozen times a day for several years to a few attacks which almost pass unobserved. The flashes (also called flushes) seem to be a most dependable indication of the cessation of normal ovarian function. In many

<sup>1763</sup>Lewis T F Symposium Menopausal Disorders, *Rev M Progr* pp 22-27 1940

<sup>1764</sup>Frank R T Goldberger M A and Salmon L J The Menopausal Syndrome, Hormonal Status and Treatment, *New York State J Med* 52: 1-9 1950

<sup>1765</sup>Van Hoesen E Laboratory Diagnosis of Menopausal and Ovariolethal States, *Rev M Progr* 10: 90-92, 1940

<sup>1766</sup>Haikinson L F Menopausal Syndrome, 1,000 Consecutive Patients Treated With Estrogen, *J A M A* 111: 360-363, 1933

<sup>1767</sup>McDermid J H and Patterson A S Physical and Psychologic Symptoms of the Menopause, *J Obst & Gynec Brit Emp* 47: 319-326, 1940

cases in which deep X ray therapy was directed to still functioning ovaries mostly because of pelvic malignancy the author hardly ever observed the onset of the induced menopause without flushes. On the other hand if flushes failed to be noticed the sterilization was usually not accomplished. Reynolds showed that the menopausal flush is caused by arteriolar dilatation. He demonstrated in plethysmographic tests that the injection of estrogen in menopausal women is followed by a plateau type of vasodilatation. This reaction does not cause any sensation. While the plateau type response is developing a sharp increase in the tested finger volume may occur and last from three to fifteen minutes. During this flush type reaction the skin temperature is elevated and the patient has a sensation of heat. Excessive perspiration and formication is a complaint in about one third of the cases.<sup>700</sup>

**Hypertrichosis.**—While flushes and perspiration have a physiological character a great number of dermatoses have been related to the menopause. On the borderline between physiological and pathological dermatoses is



FIG. 232. Climacteric hypertrichosis.

the hair growth which sometimes appears as a more marked lanugo on the upper lip and sometimes as more or less numerous thick dark bristles on the chin and in the ears. At the same time the hair on the scalp as well as the axillary and pubic hair loses much of its vigor and becomes scanty and thin. In rare cases the menopausal hair growth may assume the character of a true beard which embarrasses the unfortunate woman to an extreme degree. The menopausal

facial hair growth shows a remarkable similarity to the scattered "beard" of the male castrates. It seems that the functioning ovary affords a certain protection against the hair growth stimulating effect of the adrenals. In two cases of the literature menopausal facial hair growth was strongly stimulated by ovariectomy. In one of these remarkable cases the patient had to shave twice daily and in the other the woman made the best of her condition by exhibiting herself as a bearded woman in the side show of a circus.<sup>178</sup> Rosenhagen tried to solve the pathogenesis of the menopausal beard by paying special attention to this question during autopsies on women above the age of thirty. In thirty cases with marked beard growth the ovaries and adrenals were separated from fat weighed and histologically examined. In five cases adenomas of the adrenal cortex were found but the remaining twenty five did not yield any tangible findings. Perhaps the shift in the relation between the still vigorous adrenals and the atrophying ovaries suggests an explanation.<sup>179,179a</sup> But if so why does not the menopausal hypertrichosis appear more frequently? Another suggested cause is the elevated prolactin level in the blood and urine, which together with hypertrichosis, is also found in the basophile adenoma of the anterior pituitary.

**Pigmentation Benign Cutaneous Neoplasms.**—Changes in the pigmentation and chloasma resembling spots, as well as depigmentations occur quite frequently.<sup>179</sup>

Stimulation of the growth of small soft cutaneous fibromas and moles is common. It may be explained by the oversupply of prolactin. Similar phenomena can be observed in pregnant women. The so-called cutaneous tags or small fibromata pendula around the neck are very common in menopausal and especially obese women.

**Obesity**—The panniculus adiposus is very often increased. Careful study of the blood chemistry, basal metabolism etc. has so far failed to find the cause.<sup>180</sup> Some women become thinner with the change of life.

**Pruritus Vulvae Leukoplakia. Kraurosis**—Pruritus vulvae is common in the menopause. There are many causes or combinations of causes which may lead to pruritus and its related conditions. The most common irritations those caused by discharge and infected urine<sup>181</sup> do not strictly fall into the scope of this book. Oxuriasis does not seem to play a major role in vulvar pruritus of the menopause, but mycotic infection is very common in America in contrast to Europe.

Latent diabetes with or without sugar in the urine often causes pruritus vulvae.<sup>182</sup> Coincidence with the menopausal age may often cause the physician

<sup>178</sup>Kovacs, F. Beitrag zur Pathologie des Hirschen und Virilismus, Monatschr. f. Geburtsh. Gynäk. 91: 65-79, 1922.

<sup>179</sup>Berblinger W. Klinische Gesichtsbildung und endokrine Drüsen, Ztschr. f. d. ges. Anat. 3: 438 f. Konstitutionsl. 10: 413-423, 1924.

<sup>179a</sup>Berblinger W. B. Zur Frage der Gesichtsbildung bei Frauen, Ztschr. f. d. ges. Anat. Abt. 2: 438 f. Konstitutionsl. 23: 193-214, 1926.

<sup>180</sup>Kovacs, F. und Peiser M. Haar und Klimakterium, Endokrinologie 9: 8: 121, 1921.

<sup>181</sup>Marill A. Treatment, Pruritus Vulvae Brit. J. Derm. 52: 32-33, 1910.

<sup>182</sup>Wheeler L. B. and Strakosch, E. A. Vulvar Pruritus as Possible Early Symptom of Unrecognized Diabetes, Journal-Lancet 60: 423-424, 1910.

to treat such patients with hormones instead of applying more sensitive tests for detecting diabetes. It seems as though the part which the various etiologic factors have been accused of playing depends on the various authors. Still after the deduction of all the readily explainable cases of pruritus vulvæ there remains a group which can be linked to hormonal disorders as was suggested a long time ago<sup>176,177</sup> mainly because of coincidence with menstruation hypomenorrhea<sup>178</sup> and particularly the menopause and castration<sup>171,179,1799</sup>



Fig. 223. Kraurosis vulvæ.

Lately based on blood assays unexpectedly high estrogen values in the menopause have been found together with pruritic conditions of the vulva.<sup>180</sup> The frequent reports of successful treatment with estrogens have done much to establish the general opinion of a hormonal etiology.

It has been attempted to separate chronic pruritus vulvæ, leukoplakia and kraurosis. Since transitional pictures are common and the same case may in its course pass through all the varieties it is justifiable to deal with them

<sup>176</sup>Jirouq L. Kraurosis, Bull. Soc. franc. d. dermat. et syph. 1912 also Ann. de dermat. et syph. Abstr. Dermat. Wechnchr. 62 305, 1916.

<sup>177</sup>Tausig. Precancerous Lesions of the Skin of the Vulva. Leukoplakia Vulvæ Kraurosis Pruritus. Arch. Dermat. & Syph. 1 621-633, 1920.

<sup>178</sup>Ferrari A. B. Presentazione di case clinico, Olor. Ital. di dermat. 68 1466-1467 1927.

<sup>179</sup>Labhardt A. Pruritus Vulvæ. Etiology and Therapy. Abstr. of med. Wechnchr. 79 1212 1214, 1916.

<sup>1799</sup>Ferraris E. Kraurosis Vulvæ. Arch. f. Gynäk. 126 574, 1924.

<sup>180</sup>Khata, E. Degenerative V. Involat. the Associa. of With Estrogen Imbalance. J. Obst. & Gynaec. Brit. Emp. 48 482-494, 1951.

together. The disease starts with a subacute dermatitis of the vulva and often of the perianal area. There are exacerbations with oozing and widening of the involved area, followed by regressions. Secondary infection especially folliculitis and irritation from scratching is common. A certain percentage of the cases may heal in this stage while others may develop a condition which is quite different from chronic eczema. The skin which was red and succulent before gradually acquires a leathery rigid character and cracks easily. It becomes more and more depigmented pearly or bluish white and dry. The hair the labia minora and the clitoris disappear. Finally atrophy of the vulva with white thin skin develops. The introitus vaginae may become contracted. Pruritus is present in all stages, and on close inspection leukoplakia can be found in almost every instance.<sup>170</sup> It is from these leukoplakic patches that cancer develops in more than fifty per cent of the cases. The histologic picture corresponds to the described clinical sequence. Hyperkeratosis acanthosis, and inflammatory infiltration of the upper derma is followed by thinning of the epidermis, and loss of pigment and elastic fibers. The papillae disappear completely. Many patients with chronic vulvar eczema never develop leukoplakia and kraurosis and cancer is rare in these nonleukoplakic cases.

Treatment of the pruritus vulvae, based on the elimination of the mentioned etiologic factors, is not often possible. Besides various local procedures, estrogen therapy should be tried. The dosage advised has become higher and higher. Foss<sup>169</sup> starts the treatment with injections of from 10 to 25 mg of estradiol benzoate twice weekly. As improvement occurs the injections are reduced to one a week. Smaller doses are necessary if local treatment in the form of ointment containing estrone, estradiol or estradiol benzoate is used. Foss gives the following formula for the ointment:

Estradiol benzoate consisting of	10 milligrams in sesame oil mixed with 100 grams of base
Habibet liver oil	20 parts
Cerae albae	16 parts
Adipis laevis	2 parts
Sodium bicarbonate	1 part
Ol. amygdalis	41 parts
Aquae	20 parts

A great number of similar creams have been advised.<sup>169-170</sup> The massaging into the thoroughly cleansed skin of 0.5 mg. of estradiol in sesame oil seems a practical method.<sup>169</sup> This should be done once daily by the physician. Later the patient may follow it up with an estrogen cream.

<sup>169</sup>Foss, G. L. Further Developments in Treatment (Pruritus Vulvae). *J. Obst. & Gynaec. Brit. Emp.* 48: 371-355, 1939.

<sup>170</sup>Klatten, E. Treatment of Epithelial Pruritus and Eczema of Vulvae by Steroidaceous Local and Parenteral Administration of Estrogens. *J. Clin. Endocrinol.* 3: 212-213, 1942.

<sup>171</sup>Labarre, J. J. Stilbestrol (Kestrogen) Creams in Pruritus, Urol. & Cutan. Rev. 45: 314-315, 1941.

<sup>172</sup>Mykral, Robert V. Oestrogendiol (Estrogenic Preparation) in Therapy of Pruritus Vulvae, *Wien. med. Wochenschr.* 86: 605-606, 1939.

<sup>173</sup>Kerrick, A. Y. Treatment of Chronic Pruritus With Local Applications of Estrogen, *New England J. Med.* 236: 661-662, 1939.

Suppositories containing 0.36 mg. of di hydro-oxygestrin in 2 grams of cocoa butter have been found effective when inserted into the vagina once or twice daily.

It seems as if the initial enthusiasm about the hormone therapy of vulvar pruritus is subsiding.<sup>1899,1900,1901</sup> It is certain that estrogen therapy not infrequently fails. The difficulty of finding out the suitable cases has led to the unsuccessful treatment of many cases. It is furthermore agreed that only few patients achieve complete and lasting comfort. Relapses, which require further local therapy or a few injections are common. The more severe cases need almost continuous substitution therapy in one form or another.<sup>1902</sup> Some authors are reluctant to administer the estrogen locally over a long time because of the danger of producing cancer in a condition which is precancerous in itself. Finally, adverse effects like uterine bleeding in menopausal women and local exacerbations are known to occur. However, the fact remains that estrogenic therapy in many cases is one of the best methods we have for giving relief in a very annoying condition.

Similarly as in neurodermitis to which pruritus vulvae has other parallels the gastric hydrochloric acid has been found low or completely lacking in about one out of three cases. The more severe cases of kraurosis and leukoplakia are associated with achlorhydria.<sup>1903,1907</sup> These cases seem to be benefited by regular HCl medication. Vitamin A in any convenient form<sup>1908</sup> and vitamin E or wheat germ oil in very high doses<sup>1799</sup> as well as vitamin B<sub>1</sub>.<sup>1904,1906</sup> and uncooked diet have been recommended but not enough convincing experience has been forthcoming.

In discussing the internal therapy of the pruritic conditions of the vulva, the importance of the various local methods such as antipruritic salves and lotions, surgical procedures and radiation therapy should not be forgotten.

Miscellaneous.—The great number of cases of eczema herpetiform eruption, pruritic attacks and other dermatoses which have been labeled as menopausal because they appeared in women at the age of forty to fifty-five have rarely been investigated closely enough to corroborate this claim. Naegeli and Fellner<sup>191</sup> believe in a higher cutaneous sensitivity in the menopause just as is present during menstruation. This is supposed to account for many of the eczemas in middle aged women. High urinary prolactin does not prove more than the onset of the menopause and therefore does not confirm gonadal origin of the dermatosis in question. The best though still not a perfect proof is prompt cure after treatment with estrogen.<sup>191</sup>

<sup>1899</sup>W. A. Pruritus Vulvae, Leukoplakia and Kraurosis, J. Obst. & Gynaec. Brit. Emp. 69 210-237 1912.

<sup>1900</sup>R. R. Pruritus, Leukoplakia and Kraurosis in Patient Aged 63, S. Clin. North America 29: 107-116 1910.

<sup>1901</sup>W. B. H. A. Achlorhydria and Pruritus Vulvae, J. Obst. & Gynaec. Brit. Emp. 78 1053, 1913.

<sup>1902</sup>K. D. Pruritus Vulvae, Vitamin A and Vitamin B<sub>1</sub>—Complex in Therapy, Zbl. f. Gynäk. 68 923-927 1912.

<sup>1903</sup>P. H. Pruritus vulvae, Deutsche med. Wchnschr. 38 941-942 1912.

<sup>1904</sup>L. S. and L. B. Dermatosen bei Frauen auf hormonaler Grundlage, Prax. dermat. 26 212-215, 1921; Zbl. 41 79 1917.

A tendency to *edema* in various forms is an often mentioned climacteric manifestation. There are slight fugitive edemas of the extremities and also of the face which develop over night and disappear during day time.<sup>181</sup> Angioneurotic edema (Quincke's edema) is undoubtedly more common in the menopause and may then respond to hormonal therapy.

*Urticaria lactitia* and an urticarial character of various types of dermatitis is often mentioned in connection with the menopause.



FIG. 224



FIG. 225

FIGS. 224-225. *Keratoderma climactericum* Hanthausen. discrete palmar hyperkeratosis with lag absence of ridges frequently. It is obesity and hypertension following menopause. (Courtesy Dr. H. Hanthausen, Copenhagen, Denmark.)

Hanthausen<sup>181a</sup> described a *keratoderma climactericum* ten cases of a dermatosis which he observed in women who besides the symptoms of menopause showed some degree of obesity, a normal basal metabolism, arterial hypertension and occasionally arthritis.

In the early stages the skin changes consist of lentil size discrete scaly keratomes apparently without inflammation. They are seen on symmetric spots of the palms and soles. Later they can hardly be differentiated from eczema.

<sup>181</sup> Oerumkasan, H. Leber klimakterischen Oedem. *Med. Klin. BB.* 1870-1871. 1933.  
<sup>181a</sup> Hanthausen, H. Keratoderma Climactericum. *Brit. J. Derm.* 46: 161. 1954.



The relative frequency of *pemphigus* in the menopause has been emphasized.<sup>1813</sup> The author is inclined to confirm this impression.

Rosacea and telangiectases are often mentioned in connection with the menopause. The same applies to Fox Fordyce disease to Poikiloderma atrophicum vasculare, calcifications of the skin, acrodermatitis atrophicans, Raynaud's syndrome, scleroderma, erythema perstans, trophedema,<sup>1812-1819</sup> xanthelasma and other dermatoses.



Fig. 226. Kera oderna climactericum (Hartmann). From Lynch F. W. Arch. Dermat. & Syph. 1943.)

<sup>1813</sup>Wertheimer J. Pemphigus, Arch. f. Dermat. Syph. 181: 179 1920.

<sup>1814</sup>Lilroy F. W. A Undescribed Variety of Hereditary Edema, New York M. J. 88: 503 1892.

<sup>1815</sup>Lilroy F. W. Chronic Hereditary Edema, J. A. M. A. 81: 1172, 1923.

<sup>1816</sup>Chrost K. F. Xanthelasma und Ikterus, Starch u. Klin. Med. 73: 479 1911. Wien klin. Wochenschr. 23: 1630-1635 1910.

<sup>1817</sup>Adlerberg D. Beobachtungen bei einer angeborenen Xanthelasma-ose Arch. f. Dermat. Syph. 143: 500 1921.

## CHAPTER XXVI

### MISCELLANEOUS DERMATOSES WITH ENDOCRINE BACKGROUND

**Dermatitis Dysmenorrhoea Symmetrica**.—In 1912 Matzenauer and Polland<sup>118</sup> published six cases of an unusual dermatitis in dysmenorrhoea, mostly young girls. The attacks or crops were not in connection with the menses. The lesions appeared in patches which were mostly round on the trunk and more oblong on the extremities. They were approximately symmetrical except in or close to the midline. The individual lesion started with a burning sensation followed by a pale red urticarial erythema, the tinge of which was different from the early stage of ordinary dermatitis. Within half an hour the urticarial infiltration made the follicles stand out. Serum exuded into the follicles and formed a thin yellowish crust on the follicular orifice. These follicular lesions often coalesced within a few hours to form large weeping or crusty patches which were still slightly elevated because of their urticarial component, and surrounded by a narrow inflammatory margin. Follicular extravasations often gave the patch a characteristic dotted appearance. The varying intensity of the changes could produce all degrees of inflammation running the gamut of exudative and hemorrhagic stages to the severe destruction of connective tissue with scar formation. The lesions healed quickly within a few days unless deeper destruction occurred which was rare. In these cases the picture and course was that of a dry necrosis and slow demarcation caused by an anemic infarct. The patches appeared most often on the face and less often on the hands, arms, legs and upper trunk. In one case the oral and laryngeal mucosa was involved.

Looking at the pictures of the original article one cannot help thinking of artifacts produced by striking or rubbing the skin with the fingers. The authors were fully aware of this impression and did everything imaginable to rule out self-inflicted lesions.<sup>119</sup> They observed some patches developing while the patient was asleep or under impervious dressings of zinc-gelatin. The buccal and laryngeal lesions certainly could not be self-inflicted. When a lesion was observed to appear on one leg the corresponding spot of the other leg was immediately covered by a zinc-gelatin dressing. When this dressing was removed after two hours of constant medical watching a typical patch was found. It was impossible to produce typical lesions by mechanical and electrical irritation by spraying with ethyl chloride or by other methods.

All patients were suffering from *dysmenorrhoea*. The menses were irregular connected with many complaints and the flow scanty. Puberty and the onset

<sup>118</sup>Matzenauer H. and Polland, R. *Dermatitis Symmetrica Dysmenorrhoeica*, Arch. f. Dermat. Syph. 111: 245, 1912.

<sup>119</sup>Polland, R. *Neue Beiträge zur Klinik der Dermatoide dysmenorrhoea*, Arch. f. Dermat. u. Syph. 131: 483-490, 1921.

small patch hidden under the hair to the size of a whole leg. The spots are often found on the nape of the neck, on the lower back, and on the buttocks. They resemble the milk coffee spots seen in von Recklinghausen's neurofibromatosis. These areas of pigmentation indicate some relationship to the skeletal involvement. Unilateral bone disease is usually accompanied by ipsilateral pigmentations; widespread bone lesions by numerous and large pigmentations.



Fig. 222—Albright's Syndrome. Note areas of pigmentation. (Courtesy Wisconsin General Hospital.)

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<sup>47</sup>Matzenauer N., and Pollard, E. Dermatitis Symmetrica Dysmenorrhoeica. Arch. f. Dermat. u. Syph. 111: 343, 1912.

<sup>48</sup>Pollard, E. Neue Beiträge zur Klinik der Dermatitis dysmenorrhoeica. Arch. f. Dermat. u. Syph. 121: 482-490, 1921.

of menstruation had often been late in one case precocious. Psychopathic stigmata and functional circulatory disorders were noted.

There is no doubt that the syndrome described by Matzenauer and Polland is an unusual one. It must be very rare and the geographic distribution very uneven. While the six original and two of the later cases of the conspicuous dermatosis were seen in the clinic in Graz, Austria, almost all the other cases so far about forty were seen in European and American centers which handle great numbers of patients. Only part of the forty cases published so far closely resemble the original description.<sup>1819-1883</sup> The classical clinical picture of round oblong or finger-shaped symmetrical patches does not seem to be a requirement anymore since cases of various types of dermatitis associated with ovarian disorders have been published as dermatitis dysmenorrheica. This has apparently been done with the consent of Polland who in 1935 in an abstract written by him did not object to Urbach's<sup>1479-1484</sup> including some cases of erythroderma and neurodermatitis into the syndrome called Dermatitis dysmenorrheica.

This depreciation of the morphology has come about by the progress achieved in determining the etiology of the menstrual dermatoses. Urbach believes that the reactivity of the individual determines the morphology of menstrual dermatoses of a given dyshormonal causation. Thus today the term dermatitis dysmenorrheica includes various dermatoses associated with menstrual disorders.

Urbach and Kitamura<sup>1884</sup> in their case of menstrual neurodermatitis labeled as dermatitis dysmenorrheica found the urinary excretion of gonadotropic substances increased while the estrogen content of the urine appeared to be lower than normal. The patient was improved by estrogens and progesterone also by bleeding and laxatives. The effect of the latter kind of treatment suggests a toxic factor. According to Urbach it is occasionally possible to demonstrate that in dermatitis dysmenorrheica the premenstrual blood contains a substance which when injected into the skin of the patient during the intermenstruum will evoke an immediate urticarial reaction and a delayed response in the form of pinpoint-sized papules clinically resembling the menstrual dermatosis. Such a reaction could not be elicited in the patient with her own intermenstrual serum or with premenstrual serum from normal women. Normal control persons did not respond to the premenstrual serum of the patient. Probably as in the other menstrual dermatoses allergic as well as toxic, and possibly neuro-psychogenic factors may be of importance. Pregnancy and cessation of the menses

- Friedberg J. Dermatitis symmetrica dysmenorrhoeica. Arch. f. Dermat. Syph. 111: 172, 184, 1912.  
<sup>1819</sup>Wheeler F. and Parkhurst. So-called Dermatitis Dysmenorrhoeica. Arch. Dermat. & Syph. 2: 723, 1920.  
<sup>1820</sup>Wheeler F. Gibt es eine spezifisch dysmenorrhoeische Hauterkrankung? Arch. f. Dermat. u. Syph. 136: 36-47, 1922.  
<sup>1821</sup>Hack L. Beitrag zur Dermatoses symmetrica dysmenorrhoeica (M. Matzenauer-Polland). Wien. med. Wochenschr. 75: 3: 5-8, 79-83, 1925.  
<sup>1822</sup>Lindner L. Ueber die sog. Dermatitis symmetrica dysmenorrhoeica. Diss. Erlangen, 1922. Einl. 16, 906.  
<sup>1823</sup>Urbach, E. and Kitamura. Ueber pathologische Ausscheidung von Sexualhormonen bei einem Falle von Dermatitis dysmenorrhoeica. Polland (M. Matzenauer). Klin. Wochenschr. 11: 271, 274, 1935.

prevents the attacks. This has been demonstrated in several instances when after failure of other measures X ray castration was resorted to.<sup>67, 68</sup>

In several cases monthly attacks preceded the unusually late menarche and failed to appear later.<sup>69-72</sup> In two cases of symmetric dermatitis dysmenorrhea marked prolanuria could be demonstrated.<sup>67</sup>

The treatment should tend to correct any endocrine disorder. If this fails the desensitization with premenstrual blood after the methods of Geber and Lehner and Rajka should be tried (see menstruation). Estrogen salve (5000 units per gram of Aquaphor) has been claimed to be successful locally.<sup>129</sup> Castration must be reserved for severe and intractable cases.

**Fox Fordyce Disease.**—The dermatosis in question is a chronic, symmetrical papular itching eruption involving the armpits and the pubic area. The axillary lesions form a diamond-shaped palm-sized group of closely set yet discrete, firm, shotty perioral papules of pinhead to pea size. The papules are of normal or pink color, only little excoriated and mostly arranged in beaded rows which cross the axilla. These grater like rows can be well demonstrated by stretching the skin. This dermatosis is, with rare exceptions, extremely itchy so that the axillary hair is usually rubbed off. Similar lesions occur though much less often in the pubic area and in the skin of the external genitalia and the navel.<sup>130</sup>

The pathologic changes consist of acanthosis, parakeratosis, keratosis and inflammation mainly surrounding the openings and lining the ducts of the apocrine sweat glands and of the hair follicles. The orifices of the involved glands are usually blocked by a keratotic plug.

The disease is quite rare and seems to affect pigmented races more often, e.g. the Negroes and Jews (Jadassohn in discussion<sup>131</sup>). Only in a few (4) instances has it been observed in the male.<sup>132-135</sup> The eruption is almost exclusively a disease of the menarche. It has never been seen before puberty at which period it sometimes starts.<sup>136</sup> The menopause may bring the trouble to an end<sup>137</sup> but the disease may also be provoked at this time.<sup>138</sup> The dis-

<sup>130</sup>Berke K. Fall von Toxicoderma menstruale mit erysipelatoiden Eruptionen, *Orvol* *beil.* 63 301-303 1923 *Eid.* 25 435.

<sup>131</sup>Tragus J. Die dysmenorrhoeische symmetrische Dermatitis (Pellagrae Krankheit), *Rev. méd. de Barcelone* 4 525, 1925 *Eid.* 36 60 1926.

<sup>132</sup>Tragus J. Die symmetrische dysmenorrhoeische Nekrose. *Cron. méd. mens.* 24 10-14, 1926 *Eid.* 31 504 1927.

<sup>133</sup>Artas, M. Considerazioni cliniche ed anatomiche intorno alla dermatosi simmetrica dysmenorrhoeica. *Arch. ital. di derm.* 51 6 813-820 1931.

<sup>134</sup>Raifvercheid W. Zur Behandlung ovarial bedingter Dermatosen mit Follin/Hormonol.  
*München med. Wchnsch.* 91 1700 1937.

<sup>135</sup>Alexander A. Fox Fordyce'sche Krankheit. *Handb. d. H. Gk.* 6 1 422-443 1937.

<sup>136</sup>Pink, W. Zur Pathogenese der Fox Fordyce'schen Krankheit, *Arch. f. Derm.* 4 573, 1941.

<sup>137</sup>Kaufman, S. M. Fox-Fordyce's Disease in Male. *New York State J. Med.* 36 67-72, 1936.

<sup>138</sup>Geiger, Kamel, H. Fox-Fordyce-Erkrankung. *Eid.* 35 484 1935.

<sup>139</sup>Levy, Joseph S. Fox Fordyce Disease. *Arch. f. Derm.* 4 573, 1941.

<sup>140</sup>Oeri, München med. Wchnsch. 79: 823 822.

<sup>141</sup>Dawling, O. B. and Forman, L. Fox Fordyce Disease. *Proc. Roy. Soc. Med.* 36: 401-402, 1932.



Fig. 227



Fig. 228

Figs. 227-228. F. Fordyce disease. (Courtesy D. Frank Vere, Vanderbilt Clinic, New York.)

order seems to improve in pregnancy.<sup>142 147</sup> Ovarian deficiency with amenorrhea, dysmenorrhea, infantillism, cystic ovary and other sexual dysfunctions have been described in the great majority of cases.<sup>171 172-182</sup> Premenstrual and menstrual exacerbations which may climax in violent pruritic spells is often mentioned. Hyperthyroidism<sup>183</sup> and hypothyroidism<sup>184</sup> have been found much less often than ovarian deficiency.



Fig. 279.—Fox-Fordyce disease. Extremely itchy, unhealed, after x-ray treatment.

Considering the well known sexual relationship of the apocrine glands (see Puberty) and the evidence of accompanying ovarian disorders an ovarian etiology seems very probable. This is further supported by the response to estrogen therapy and in some cases prolation therapy.<sup>79 84 86</sup> Some authors believe that the condition is not curable and others think that roentgen therapy is the most effective treatment.

<sup>142</sup> Gougeon and Bism, P. Maladie de Fox-Fordyce non prurigineuse. Bull. Soc. franç. de dermat. et syph. 29: 700-701 1923.

<sup>147</sup> Lortet-Jacob and Gastinel. U. cas de maladie de Fox-Fordyce. Bull. Soc. franç. de dermat. et syph. 24 12. 329.

<sup>149</sup> Kämpf, U. Fox-Fordycesche Krankheit. Zbl. 23 124. 1921.

<sup>150</sup> Dabachew. Fox-Fordyce Disease. Arch. Dermat. & Syph. 12: 572. 1923.

<sup>151</sup> Goodman, M. H. and Solomon, M. Fox-Fordyce Disease. (Estrogenic Studies). Arch. Dermat. & Syph. 23 967 1929.

<sup>152</sup> Sarg, J. Hormonal Dysfunction in Fox-Fordyce Disease. Oregon Med. 32: 346-350 1926. Amer. Dermat. Assoc. 27 124-127 1924.

<sup>153</sup> Aramark, S. La maladie de Fox-Fordyce. Ann. d. dermat. et syph. 9: 529 1921.

<sup>154</sup> David, F. Corpus Luteum Hormone Therapy. Practise (Lancet) 22 March, med. Wimmer. 87: 42-43 1940.

<sup>155</sup> Rosenberg, A. C. A Case of Fox-Fordyce Disease. Brit. J. Derm. 55: 121 1943.

<sup>156</sup> Kirtles, E. Sex Hormones in Therapy of Fox-Fordyce Disease. Dermat. Wochenschr. 123: 723-726 1941.



**Albright's Syndrome**—This typical combination was first recognized by Fuller Albright<sup>1847</sup> who described a triad of disseminated osteitis fibrosa areas of cutaneous pigmentation which have a distribution suggesting some connec-

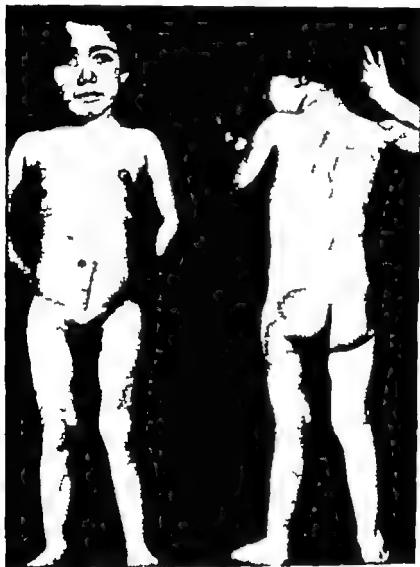


FIG. 230 Albright's syndrome. Areas of pigmentation and precocious puberty. (From Albright F. In: Lee A. M., Hampton A. O. and Smith P. New England J. Med.)

tion between them and the bone lesions and sexual and somatic precocity when the disease occurs in the female sex." Pathological fractures are common

<sup>1847</sup>Albright F. In: Lee A. M., Hampton A. O. and Smith P. Osteitis Fibrosa Disseminata. Areas of Pigmentation and Endocrine Dysfunction With Precocious Puberty in Females. New England J. Med. 216: 727-744, 1937.

According to Lichtenstein and Jaffe<sup>144</sup> who reviewed ninety cases among them fifteen of their own the syndrome is not extremely rare if one includes the incomplete cases. The disease affects girls more often than boys the ratio being about 3:2. The first symptom is often a pathological fracture which leads to x-ray examination of the bones. Scattered but often unilateral patchy cystlike lesions of osteitis fibrosa are found. There are always parts of the skeleton showing normal bones.<sup>144, 145</sup>



Fig. 22. Albright's syndrome. Osteitis fibrosa disseminata. From Albright, P. New England J. Med.

In the female sex usually previous with early onset of menstruation and development of secondary sex characteristics and early bone age occurs in about one third of the cases.<sup>146</sup> The sexual development in the male patients is normal. In the skin there are smooth brown nevus like patches of oblong round or irregular shape. These arise in size from a group of freckle like spots or a single

<sup>144</sup>Lichtenstein, I. and Jaffe, H. L. Fibrous Dysplasia of Bone Condition Affecting One, Several or Two Bones. In: *Endocrinology*, W. B. Saunders, Philadelphia, 1933, 777, p. 813.

<sup>145</sup>Albright, L. W. Differential Diagnosis of Hyperparathyroidism With Especial Reference to Albright's Syndrome. New York, J. Med. 43, 1-4, 1944.

<sup>146</sup>Albright, L. W., Campbell, S. M., and W. Denhamer, L. and Reid, N. R. Albright's Syndrome. *Endocrinology*, 1945, 28, 2.

small patch hidden under the hair to the size of a whole leg. The spots are often found on the nape of the neck, on the lower back, and on the buttocks. They resemble the milk coffee spots seen in von Recklinghausen's neurofibromatosis. These areas of pigmentation indicate some relationship to the skeletal involvement. Unilateral bone disease is usually accompanied by ipsilateral pigmentations; widespread bone lesions by numerous and large pigmentations.



FIG. 231 Albright's syndrome. Not area of pigmentation. (Courtesy Wisconsin General Hospital.)

The blood calcium and blood phosphorus are normal; this is important in the differentiation of hyperparathyroidism. In spite of at least twenty-five recorded explorative operations, a parathyroid tumor has never been found. The differential diagnosis has to rule out neurofibromatosis, Hand-Schüller-Christian's xanthomatosis, Paget's disease, multiple hemangiomas of the bones and some other rare condition. The diagnosis is easy if the classic triad of bone disease, pig-

mentation and precocity in the female is present. Several patients started life with icterus gravis neonatorum which persisted for months.<sup>100 101</sup>

The etiology is unknown. An embryonic defect (Albright) seems likely. The twin brother of one patient was normal. In some cases a positive Babinski suggests a participation of the nervous system.<sup>102</sup>

The prognosis of the disease should be guarded but not too pessimistic. In one case precocious puberty was followed by normal adult sex life with the consequent production of a healthy child. The bone disease may become arrested. The individual bone lesion is amenable to surgical treatment.

It is of interest that Lena Medina of Peru who gave birth to a child at the age of five probably represented such a case of Albright's syndrome. Her attending physician Dr Gerardo Lozada of Pisco Peru informed Dr Albright that she had both the brown spots and bone changes together with the precocity.

**Geroderma Genito-Dystrophicum Progeria.**—In this rare syndrome which has been seen starting early in life in both sexes the most striking feature is the senile appearance of the skin and particularly of the face. There are many fine wrinkles the skin is flaccid yellowish and the subcutaneous fat and the muscles on the distal parts of the extremities are usually extremely reduced. The hair is either completely lacking or restricted to the scalp. The skin gives a senile atrophic impression which make children or relatively young persons look old. Diffuse and early arteriosclerosis is a characteristic feature. Generalized pigmentation has been seen. The nails are thin and brittle. The skeleton is either eunuchoid or dwarfed. The intelligence is intact. Many endocrine symptoms like diabetes insipidus, exophthalmos, polyphagia and amenorrhea have been described. The testicles are atrophic. Aplasia or atrophy of the thyroid and tumor or sclerosis of the pituitary have been found at autopsy. The disorder is probably related to Simmonds' disease in which precocious senility is also a feature.<sup>103</sup> In spite of the severe changes the mentality remains alert and the patients may live for many years.<sup>104-105</sup> A syndrome of infantilism with web formation of the skin along the neck is known as *Turner's*<sup>106</sup> syndrome. In one autopsy case<sup>107</sup> no functioning ovarian tissue could be found. There was no axillary hair present and the pubic hair was scanty.

**Scleroderma, Poikiloderma, Acrodermatitis Atrophicans.**—The voluminous literature on these rare dermatoses is replete of reports on accompany

<sup>100</sup>Brick, F. Osteose Dystrophy Following Icterus Gravis Neonatorum, Arch Dis Childhood 11 181-203, 1936

<sup>101</sup>Baumertfeldt, F. and Brews, A. Osteodystrophia fibrosa, Am. J. Dis Child. 57 90-101 1939

<sup>102</sup>Dockerty, M. B. Myerding, H. W. and Wallace, O. T. Albright's Syndrome, Proc. Staff Meet. Mayo Clinic 19 81-85, 1944.

<sup>103</sup>Overström, H. Die Simmondsche Krankheit, Med. Klin. 28 306-307 1933.

<sup>104</sup>Marinone, G. and Parhon, O. L. Sur un cas de diabète insipide avec cachexie hypophysaire infantile et atrophie atrophie des organes génitaux et convulsions d type épileptique. Rev. franc. d'endocrinol. 10 108-148, 1933.

<sup>105</sup>Thakkester, S. J. Werner's Syndrome (Progeria of the Adult) and Reckstein Syndrome, Ann. Int. Med. 11 840-846, 1943.

<sup>106</sup>Turner H. H. A Syndrome of Infantilism, Congenital Webbed Neck and Cubitus Varus, Radiology 22 868-874, 1933.

<sup>107</sup>Barney-Schuler, E. F. Pterygoacral Infantilism (Turner's Syndrome) With Postmortem Findings, Lancet 21 832-880, 1961.

ing and often contradictory endocrine symptoms although no definite relationship has evolved. In *scleroderma* the most frequently observed and best founded systemic relationship is a disturbance of the *calcium* metabolism. Thibierge and Weissenbach<sup>186</sup> demonstrated calcium deposits in the sclerodermatic skin. Later this observation was often confirmed<sup>186, 188</sup> but its significance denied again more recently.<sup>189</sup> The blood calcium and also the phosphorus were often found to be above normal<sup>189-190</sup> and the tolerance to calcium expressed by the ability to restore the normal calcium level in the blood after injection of calcium was found disturbed.<sup>187</sup> Both calcium and phosphorus are retained in the body in *scleroderma*<sup>188</sup> which is not in line with the negative calcium balance in hyperparathyroidism to which the relation seemed suggestive.<sup>188</sup> The Hamilton Schwartz test for parathyroid hormone showed high values in the circulating blood in two out of three cases of so-called *Werner's syndrome* (adult progeria). This syndrome is a rare heredo-familial disease in which *scleroderma*, blue sclerae, hypogonadism, trophic ulcers, metastatic calcification, osteoöbrosis and other endocrine stigmata are the main features.<sup>188-189</sup> The Hamilton Schwartz test was negative in two ordinary cases of *scleroderma*.<sup>187</sup> There is some evidence in support of hypoparathyroidism in *scleroderma*<sup>191</sup> in the rare cases of its association with tetany.

Primary atrophic and absorptive changes<sup>173, 175</sup> prior to the *scleroderma* in the *phalanges* and in the distal ends of other bones<sup>174</sup> *osteomalacia*.<sup>174, 176</sup>

<sup>186</sup>Thibierge and Weissenbach. Concrétions calciques sous-cutanées et sclérodermie. *Ann. de dermat. et syph.* p. 129, 1911.

<sup>187</sup>Kennedy R. L. J. Calcium and Scleroderma. Treatment by ketogenic Diet. *J. Pediat.* 1: 667-672, 1932.

<sup>188</sup>Pa-trier L. M. Sclérodermes, chloïdes et calcémo, *Presse méd.* 41: 345-347, 1932.

<sup>189</sup>Kaeber H. and Schaefer H. W. Ca-Gehalt normaler Haut verglichen mit den Befunden bei Scleroderma. *Klin. Wchnschr.* 19: 352-354, 1940.

<sup>190</sup>Jung A. and Hahli, A. C. Étude sur la calcémie. *Rev. de chir.* 61: 537-548, 1933.

<sup>191</sup>Illmann H. Beitrag zur Kenntnis der Sclerodermie. *Dtsch. Hamburg* 1930.

<sup>192</sup>Leiche R. J. Og. A., and DeBakey M. The Surgical Treatment of Scleroderma. Sympathecetomy and Parathyroidectomy. 26 Cases, *Surgery* 11: 6, 1927.

<sup>193</sup>Corbuelet, T. and Struck H. C. Calcium Metabolism in Scleroderma, *Arch. Derm. & Syph.* 23: 133, 1937.

<sup>194</sup>Rothman R. and Weiss, I. Calciumbelastungsproben bei Sclerodermie. *Klin. Wchnschr.* 19: 1545-1548, 1931.

<sup>195</sup>Darrach, H. E. Scleroderma. Symposium, New Orleans M. & S. J. 92: 19-21, 1939.

<sup>196</sup>Oppenheimer B. B. and Kugel V. H. Werner Syndrome. *Am. J. M. Sc.* 262: 679-612, 1911.

<sup>197</sup>Winer V. H. The Hamilton-Schwartz Test and Hyperparathyroidism in Various Diseases, *Am. J. M. Sc.* 263: 615-630, 1921.

<sup>198</sup>Almon H. Sclérodermie et parathyroïdes, *Gaz. d. hôp.* 108: 875, 1929.

<sup>199</sup>Barnoy T. and Frisch, E. Beiträge zur Röntgenologie der Akroöbrosen. *Fortschr. d. Geb. d. Röntgenstrahlen* 47: 297-299, 1933.

<sup>200</sup>Leiche R. and Jung A. Nature et origine de la sclérodermie. *Bull. Soc. franc. d. dermat. et syph.* 42: 845-892, 1935.

<sup>201</sup>Lehon J. M. nouveaux Favregeule and Georges C. cas de sclérodermie très gros tubercles de laméfaction. Rôle des parathyroïdes. *Bull. et mém. Soc. méd. d. hôp. de Paris* 53: 921-929, 1927.

<sup>202</sup>Mars-Jocke J. L. cas de maladie de Basedow associée à la sclérodermie et à l'ostéomalacie. *Rev. neur.* 1: 2: 227, 1929.

<sup>203</sup>Stierling W. Der Hypodystrophische und der osteomalische Typus der generalisierenden Scleroderma. *Ann. Polak. gaz. lek.* 7: 86-103, 1928. *Zbl.* 27: 181.

*bilateral cataract*<sup>1006-1077-1079</sup> the experimental production of scleroderma like skin changes in young rats and pigs following injection of parathormone<sup>1080-1121</sup> and finally the relatively successful *treatment of scleroderma by unilateral parathyroidectomy*<sup>1081-1122-1123</sup> have given support to a *hyperparathyroid* etiology especially since some of the excised parathyroids were found hypertrophied or inflamed<sup>1124</sup> However the results of parathyroidectomy are still controversial.<sup>1125</sup>

There are many observations suggesting *other endocrine dysfunctions* Amenorrhea dysmenorrhea<sup>1086-1088-1089</sup> onset of the disease in pregnancy and in the spontaneous and induced menopause<sup>736-809-938</sup> findings of ovarian changes the therapeutic success of estrogens,<sup>993-1126</sup> and the 3:1 predominance of the female sex<sup>1090</sup> are reasons enough to consider the *gonads* The situation is similar with regard to the pancreas thyroid<sup>987</sup> and pituitary It is now generally accepted that *acrosclerosis*<sup>1091</sup> or *sclerodactylia* is essentially different from the diffuse or localized scleroderma (morphea) According to Sells<sup>1092</sup> *acrosclerosis* is a *vegetative nervous* and is related to Raynaud's disease True *scleroderma* however seems more likely to be a *fermentative* disorder related to the *pancreas* It has in some instances been successfully treated with pancreas liver stomach and duodenum extracts (Sells<sup>1093</sup> and many other articles by the same author)

<sup>1077</sup>Krebs, E., Hartmann, E., and Thibaut, P. III cas familial de syndrome de sclérodémie avec cataracte, troubles endocriniens et neuro-vegetatifs associés, Rev. génér. 2 608-618 1930 Ed. 264 212.

<sup>1078</sup>Maguery, A., Faury, A. and Miasse, H. Syndrome tardif de sclérodémie avec cataracte, associé à des troubles endocriniens. Bull. et mémo. Soc. méde. Hôp. d. Paris 66 281, 1930.

<sup>1079</sup>Eguchi, H. Cataract bei parathyroidectomierten Inaktivitäre bei Scleroderma. Acta Soc. ophthal. Jap. 36 167 1931 Ed. 28 633.

<sup>1080</sup>Rebel, J. Sclerodermis verum und Akroscleiose. Verh. 8 Internat. Congr. Dermat. 21 789, 1923 Ed. 63: 62, 1926.

<sup>1081</sup>Leriche, R., Jung, A. and Barvys, G. La peau dans l'hyperparathyroïdisme expérimental. Sclérodémie expérimentale. Presse méd. 2 777 1932.

<sup>1082</sup>Wassersbach, R. J., Gattelier, J. and Durupt, A. Sclérodémie progressive et parathyroïdectomie. Bull. Soc. franç. de dermat. et syph. 49: 1430-1448, 1932.

<sup>1083</sup>Garlock, J. H. Parathyroidectomy for Raynaud's Disease and Scleroderma. S. Clin. North America, 24 77 1936.

<sup>1084</sup>Daesch, G. H., Lefthof, B., Durupt, A. and Daesch, M. Sclérodémie avec contractions esclaires syndromes d. Thibierge-Wassersbach) associée à une atrophie cutanée. Parathyroïdectomie. Bull. et mémo. d. Hôp. de Paris 66: 618-631 1934.

<sup>1085</sup>Berthelin, A. R. and Garlock, J. H. Parathyroidectomy for Raynaud's Disease and Scleroderma. Ann. Surg. 161 1012, 1935.

<sup>1086</sup>Liberation, H. G. and Tardieu, P. A. Ein Fall von schwerer Scleroderma. Wien. klin. Wchschr. 45 1 10-1445 1933.

<sup>1087</sup>Grybowski, Scleroderma diffusum, Sclerodactylia, ad Scleromyxoida Ed. 26 461 1930.

<sup>1088</sup>Das-Friedman, S. Degenerative pseudo-scleroderma. Warsaw. Cas. lek. 2 127 1925 Ed. 28 578 1936.

<sup>1089</sup>Spitzer, R. Scleroderma ad Paralysis bei Gravität und Menstruation. Ed. 17 370, 1925.

<sup>1090</sup>Talbot, A. Scleroderma et puer de la peau (Etat physiopathologique) Strasbourg méde. (pt. 2) 83 307-328, 1927 Ed. 28 86.

<sup>1091</sup>Schönfeld, Scleroderma, Ed. 22: 812.

<sup>1092</sup>Lisner, K. Scleroderma Ed. 24 657.

<sup>1093</sup>Hartner, P. and Lichtwitz, A. Scleroderma Ed. 20: 225 1929.

<sup>1094</sup>Wells. Scleroderma-Sclerodactylia Ed. 26: 447.

<sup>1095</sup>Maguery, A. and Horowitz. Treatment of Scleroderma With Ovarian Hormone and Anticancer therapy. Bull. Soc. franç. de dermat. et syph. 41 64-71 1934 Abstr., Dermat. Ztschr. 70 1 1 1934.

<sup>1096</sup>Krassman, S. and Urbauer, M. Scleroderma. Handb. d. H. Ok. 8. 2 717-822 1931.

<sup>1097</sup>Rothmann, S. Endokrine Störungen bei Scleroderma. Klin. Wchschr. 4 1991 1933.

<sup>1098</sup>Rebel, J. Sclerodactylia progressive Scleroderma (Akroscleiose) Dermat. Ztschr. 58 138-144, 1932.

ing and often contradictory endocrine symptom although no definite relation has yet evolved. In *stiff skin* the most frequently observed and best founded systemic relationship is a disturbance of the calcium metabolism. Thibierge and Weissbach<sup>14</sup> demonstrated calcium deposits in the sclerodermatic skin. Later this observation was often confirmed<sup>15-16</sup> but its significance denied again more recently.<sup>17</sup> The blood calcium and also the phosphorus were often found to be above normal<sup>18-19</sup> and the tolerance to calcium expressed by the ability to restore the normal calcium level in the blood after injection of calcium was found disturbed.<sup>20</sup> Both calcium and phosphorus are retained in the body in *scleroderma*<sup>21</sup> which is not in line with the negative calcium balance in hyperparathyroidism which the latter situation seemed suggestive.<sup>22</sup> The Hamilton-Schwartz test for parathyroid hormone showed high values in the circulating blood in two out of three cases of so-called *Heber's syndrome* (adult progenia). This syndrome is a rare hereditary familial disease in which scleroderma, blue sclerae, hypoparathyroidism, cleft ulcers, metastatic calcification osteofibrous and other endocrine stigmata are the main features.<sup>23-24</sup> The Hamilton-Schwartz test was negative in the ordinary cases of scleroderma. There is some evidence in support of hypoparathyroidism in scleroderma<sup>25</sup> in the rare cases of it a confusion with tetany.

Finally atrophy and absorptive changes<sup>26-27</sup> precede the scleroderma in the pharynx and in the distal end of the bones *osteomalacia*<sup>28-29</sup>

<sup>14</sup>Thibierge and Weissbach: *sur les lésions calciques non-ostéofibroses de l'ectodermite* A. de Derm. et S. 3 p. 79.

<sup>15</sup>Korman: B. I. J. Abnormalities of Scleroderma: Their origin by histologic Diet. J. Pediat. 1: 667-672 1932.

<sup>16</sup>Levy: L. M. Scleroderma: Abnormalities of calcium metabolism. Brit. J. Derm. 41: 215-217 1932.

<sup>17</sup>Koster H. and Koster H. W. Gehalt normaler Harn-Extrakte mit den Befunden bei Scleroderma. H. W. Koster 1931 33: 1-100.

<sup>18</sup>Ng A. and Hall J. S. F. Serum calcium in calcinosis. Rev. de rhum. 81: 237-2 1932.

<sup>19</sup>Hilsmann H. Die rasche bei der Scleroderma. Derm. H. 1930.

<sup>20</sup>Leriche R. J. and Lelland M. The typical Triad seen of Scleroderma: hypoparathyroidism and Parathyroidism. N. Y. Med. Socy. 5: 1937.

<sup>21</sup>Leriche R. and Lelland M. Calcium Metabolism in Scleroderma. Arch. Derm. & Syph. 33: 1-17.

<sup>22</sup>Kothman S. and Weiss J. Abnormalities associated with Scleroderma. H. W. Koster 1931 33: 5-100 1931.

<sup>23</sup>Hampton E. Scleroderma: report on two cases. N. Y. J. Med. 2: 211 1939.

<sup>24</sup>Hyperparathyroidism: report on two cases. N. Y. J. Med. 2: 211 1939.

<sup>25</sup>Hampton E. J. The Hamilton-Schwartz Test and Hyperparathyroidism in Various Diseases. Am. J. Med. Sci. 1937 40.

<sup>26</sup>Almon H. Scleroderma et parathyroidisme. Arch. Derm. 103: 272 1929.

<sup>27</sup>Leriche R. and Lelland M. Histologie der Scleroderma. Fortsch. d. Med. 1931 67: 24-293 1931.

<sup>28</sup>Leriche R. and Lelland M. S. et origine de la scleroderma. B. H. Soc. franc. de dermat. et syph. 42: 542 1933.

<sup>29</sup>Lelland M. et Leriche R. Les lésions de l'os (cas de scleroderma) et gros troubles de l'ostéocalcémie. H. W. Koster 1931 33: 1-100 1931.

<sup>30</sup>Lelland M. et Leriche R. Les lésions de l'os (cas de scleroderma) et gros troubles de l'ostéocalcémie. H. W. Koster 1931 33: 1-100 1931.

<sup>31</sup>Hampton E. The Hamilton-Schwartz Test and Hyperparathyroidism in Various Diseases. Am. J. Med. Sci. 1937 40.

Among the many endocrine symptoms which have been reported in connection with the rare *perikloderma atrophicans vasculare* the relatively frequent onset in the *menopausis* seems worthy of mention.<sup>170</sup> The same is true of *acrodermatitis atrophicans*. In this dermatosis which is not very rare in some parts of Europe the females outnumber the males 2:1.<sup>182</sup> There are some observations of *acrodermatitis atrophicans* in Graves disease.<sup>18</sup>

**Acrocyanosis**—*Erythema venosum*<sup>183</sup> *Erythrocyanosis symmetrica*<sup>173</sup>  
*Erythrocyanose symétrique malléolaire des jeunes filles*

Symmetrical sometimes circular palm-axial cyanotic plaques almost exclusively occurring in young girls<sup>183</sup> have been described under several names.<sup>184</sup> The plaques are mostly seen anteriorly or laterally on the lower legs, less often on the inner aspects of the thighs right above the knees. The lesions are bluish red sometimes with bright red (cinnabar) spots<sup>185</sup> and some thin telangiectases. The erythema vanishes on pressure. The skin is taut and cannot be folded. The lanugo has usually disappeared. There is an ill-defined deep firmness which gives a doughy impression though there is no pitting. The lesions are cooler to the touch than the normal skin. Superficial ulceration has been seen but this is rare.<sup>185,186</sup> Local fat increase has been described.<sup>186</sup> There is only minimal nonspecific inflammation around the vessels. Capillaroscopy reveals varicosities of the capillary veins and frequent spasm.<sup>186</sup> The course is an extremely chronic one. The lesions appear in the winter time, improve in summer to some extent and reappear with the first frost. Like many lower leg conditions they are better after a night's rest and worse again in the evening. The dermatosis is clinically closely related to chilblains from which it differs in the site and the accompanying circumstances which make an ovarian relation probable.<sup>186</sup> The patients are overwhelmingly young girls and women up to about thirty years of age.

Children do not seem to become affected though they are very susceptible to chilblains. Irregularities of menstruation,<sup>183</sup> obesity<sup>186</sup> and other endocrine

<sup>170</sup>Jassier M. and Löwenstamm A. Bericht über 86 Fälle von Akrodermatitis chronica trophica, Dermat. Wchnschr. 75: 1180 1924.

<sup>171</sup>Bowen R. and Berlin E. Ätiologie der Akrodermatitis atrophicans Hehrleiner. Klin. Wchnschr. 32: 378-377 1923.

<sup>172</sup>Boardman W. P. Schröderma. Arch. Dermat. & Syph. 19: 801-816, 1928.

<sup>173</sup>Ochser A. and DeBakey M. Peripheral Vascular Disease Treatment Surg., Gynec. & Obst. 79: 1058-1072, 1940.

<sup>174</sup>Ochser A. and DeBakey M. Schröderma, New Orleans M. & S. J. 62: 13-24, 1932.

<sup>175</sup>Langhans Erythema venosum, Mischow. Med. Wchnschr. 67: 902, 1930.

<sup>176</sup>Del P. Erythrocyanose cutis symmetrica, Klin. Wchnschr. 1: 578-580, 1922.

<sup>177</sup>Umo A. Erythro-cyanose symétrique des malléolaires des jeunes filles, Thèse de Strasbourg, 1939.

<sup>178</sup>Nicola J. and Frenschard Ch. Erythro-cyanose symétrique des malléolaires des jeunes filles. Nouvelle pratique dermatologique, Vol. 8, Paris, 1936, Masson & Co, pp. 323-363.

<sup>179</sup>Loriat-Jacob, Bolesta, G. and le Baron Erythro-cyanose des membres inférieurs. Présence de taches rosées. Leur prévention efficace. Bull. Soc. franç. de dermat. et syph. 29: 1290-1291 1931.

<sup>180</sup>Dei T. Stanziosidermatite, Ed. 63: 903.

<sup>181</sup>Cardelli L. Osservazioni alla cuccovana del fascioma di artroclausa degli arti inferiori. Oler. Ital. di dermat. e sif. 66: 51 1928.

<sup>182</sup>Kridlag Akrocyanosis cruris Ed. 23: 416, 1930.

<sup>183</sup>Devi and Löwenstamm Erythrocyanose extremitatis chronica, Arch. f. Dermat. Syph. 190: 277 1925.



stigmata like hyperhidrosis of palm and soles. Marfan's<sup>100</sup> main hypogonitake dry skin, goiter<sup>101</sup> and adrenal hypotenism<sup>102</sup> have often been observed.<sup>103,104,105</sup> The condition has also been seen after castration<sup>106</sup>. F.rogen therapy and thyroid have been helpful in many cases. Yet no entirely convincing endocrinological relation has as far been established. "Tuberculosis" has been considered since some cases developed into tuberculous indurativa<sup>107</sup>. The condition seems to be rarer in the United States than in the corresponding climates in Europe.

<sup>100</sup>Marfan (1). The Hyperplasia of Hand. *Chirurgische Klin. Berl.* 63: 672-673, 1921. Zbl. 27: 279.

<sup>101</sup>Thomas, E. L. *Artery disease of the peripheral circulation*. Arch. Int. Med. 21: 193-195, 1921. Zbl. 27: 812.

<sup>102</sup>Smith, J. L. *Arteriosclerosis peripherica des jungen subjekts*. Arch. de med. d. nat. 25: 645, 1924. Zbl. 28: 197.

<sup>103</sup>Galani, J. Fall Hyperostose des Halses. Arch. f. path. Anat. 207: 81-813, 1925.  
<sup>104</sup>Galani, J. and Wilms, F. [Arteriosclerosis des jungen Menschen. Interpretation pathologische histologische und klinische] *hypertension, atherosclerosis und des hypertensiven arterien*. Arch. d. med. d. nat. 25: 78, 1925. Zbl. 31: 225.

<sup>105</sup>Forster, M. *Miscellaneous Diseases*. *Stet. 24: 79, 7, 1926.*  
<sup>106</sup>Forster, E. Les art. blanches inférieures des inférieurs des art. hypertensives des post-vascular. *Arch. de med. d. nat.* 25: 347-351, 1926.

<sup>107</sup>Galani, J. and Marfan, J. *Chirurgische Klin. Berl.* 63: 672-673, 1921. Zbl. 27: 279.

## CHAPTER XXVII

### AGEING\*

Senile atrophy of the skin starts shortly after the age of forty<sup>1366</sup> The epidermis becomes thinner at the expense of the lower strata. The horny layer appears looser. The mitoses in the basal layer become scarcer or disappear completely and the cells of the basal and prickle cell layers show perinuclear vacuolization. The stratum granulosum is hardly discernible.<sup>1367</sup> The papillae flatten and lose their elastic fibers. The collagenous fibers grow thinner and stain poorly. The elastic fibers show clumping shortening thickening and irregular positions together with marked hyperplasia especially in the face and neck. This hyperplasia of the elastic tissue may account for the yellowish tinge of the face and hands in some old people.<sup>1368</sup>

Elastin, collastin and collatin are often present.<sup>1367</sup> The peculiar accumulations of elastic fibers in the facial skin known as elastica numida<sup>1369</sup> which develop at puberty and reach their highest development at thirty are definitely regressive at forty. At sixty the alterations of the elastica are marked.<sup>1368</sup> The elastic fibers of the blood vessels especially of the elastica interna, participate in the changes. The senile changes in the elastic fibers seem to depend on exposure to light and elements, since they were not found in unexposed skin of old people.<sup>1370</sup>

Extravasation on slight trauma (*purpura senilis*) is common.

Severe arteriosclerotic changes may be observed along with corresponding senile changes in other organs.

The sebaceous glands are reduced in number and they show certain qualitative changes. In the face especially on the nose and forehead hyperplasia of the sebaceous glands is common after the age of forty. The hair follicles are often found without hair and the muscoli arrectores pilorum are usually atrophic. The subcutaneous fat shows degeneration.<sup>1367</sup> The water content of the senile skin is reduced<sup>1371-1372</sup> and the rate of insensible perspiration is lower than in young subjects.<sup>1373</sup> The capillary reactivity to mechanical and other stimuli

\*See table at the end of the book.

<sup>1366</sup>Kramak, R., Cowdry, E. V. and Kligman, P. E. Aging of Human Skin. Influence of Dermal Changes on Appearance of Epidermis in Young and Old Faced Timmes, *Anat. Rec.* 88: 343-365, 1943.

<sup>1367</sup>Cowdry, E. V. editor. Problems of Aging, ed. 2, Baltimore 1942. Williams and Wilkins Co. Chapter on skin by F. D. Weidman.

<sup>1368</sup>Kusnets, M. Changes in the Senile Skin, *Ukrain med. Arch.* 6: 1-8, 21: 109, 1932. 22d: 48, 69.

<sup>1369</sup>Ueda, I. Differences in the Elastic Fibers of the Skin According to Sex and Age, *Jap. J. Dermat. & Urol.* 66: 216, 2: 7, 1936. *Abstr. Arch. Dermat.* 87: 661, 1938.

<sup>1370</sup>Hill, W. H. and Moutonovsky, H. Regional Changes and Changes Caused by Age in Normal Skin, *J. Invest. Dermat.* 2: 23: 343, 1940.

<sup>1371</sup>Harger, M. and Schlemke, O. Chemische Gewebeanalyse für die Altersforschung, *Klin. Wchnschr.* 21: 1944-1945, 1939.

<sup>1372</sup>Barck, O. E., Cohn, A. E. and Neumann, O. Rate of Water Loss From Finger Tips and Toe Tips in Normal, Psoriasis, etc. *Am. Heart J.* 23: 183-190, 1942.

is slow in response and slow in return to the normal state.<sup>119 120</sup> Cavallucci who systematically studied the physiological reactions of the senile skin in comparison with that of the middle aged found red dermographism delayed and urticaria factitia less frequent and less pronounced. Marfan's sign (see thyroid) the pilomotor reaction and the urticarial intracutaneous morphine reaction are also less marked. Senile atrophy causes decrease of the sensitivity to touch pain and temperature. The fact that old people suffer from cold more than young persons is not due to increased sensitivity but to other probably vascular factors.



Fig. 72. *Peripara orallia*

The cutaneous manifestation of ageing are of practical importance for the objective determination of the age.<sup>121 122</sup> At the age of 20 the facial skin is still free of wrinkles. The cheeks are rounded so that the mouth and nose appear small. At 25 the forehead and the lower lid show the first wrinkles and the nasolabial fold become apparent. The veins of the back of the hand begin to show.<sup>123</sup> At 30 crow's feet appear at the lateral angles of the eyes. The beard growth is most vigorous between 30 and 40. At this age men often become more hairy on the chest, arms, and the dorsa of the hands. The occipital hairline loses its sharpness.

The thirty-fifth year usually marks the first folds in front of the ears. (Nude-shdin after Sebastiany<sup>124</sup>). These preauricular wrinkles increase in length more than in depth so that some criminologists have attributed much importance just to the length of these folds.<sup>125</sup> Graying of the hair at the temples and a less

<sup>119</sup>Jellmann, R. Altersveränderungen im Gefäßendabschnitt der Lippenchilrinnhaut, *Klin. f. Anat. Ex. verh. Jg. 62* 400-477 1930. Ed. 27: 600.

<sup>120</sup>Cavallucci, U. Anatomia. Setopateologia della cute. Reattività della cute senile. *Glor. Ital. dermat. ed. 75* 875-879 1934.

<sup>121</sup>Sebastiany, Y. Ueber objektive Altersschätzung am lebenden Erwachsenen, *Die Naem.* 1917.

<sup>122</sup>Jellier, L. R. Altersschätzung des Menschen, Berlin, 1922. Julius Springer.

rosy and more ruddy hue of the cheeks may become noticeable in the fourth decade. The age of graying varies widely. A familial factor can often be recognized.

A person of 40 already has most of the typical wrinkles. The preauricular wrinkles are now multiple and extend upward to the upper level of the tragus. The cervical folds, which run from the chin down to the jugulum, may be seen in lateral light.

At 45 the suborbital wrinkles become more marked. In light coming from the side the cervical folds can now be clearly seen. The lips start to become thinner. In a fat person the double chin is marked and in a lean person the cervical skin becomes too wide.<sup>98</sup> The eyebrows may become bushy or at least a few long hairs may grow.



Fig. 234.



Fig. 235.

Fig. 234.—Female aged 65 years. Long ear preauricular wrinkles.

Fig. 235.—Cervical and other folds and wrinkles.

In the early fifties all the wrinkles grow deeper. The hands become wrinkled. Small wrinkles of the bridge of the nose, of the ear lobe, and of the chin are present. The entire skin is now relatively dry. The graying of the hair can no longer be concealed by pulling out of the white hairs.

Senile hyperpigmentation starts around 55. Wrinkles on the bridge of the nose, the ear lobes and the chin become marked. The longitudinal cervical folds are accented. The rhomboidal crossing folds in the nape of the neck (*Cutis rhomboidalis*) are seen in some men, especially those who live an outdoor life.

In the sixth decade the teeth appear to be longer because of atrophy of the alveolar ridge.

At 60 th first radial wrinkles around the mouth appear on the upper lip. The cheek become loose and droopy. The glans penis becomes smaller and the penile skin wrinkled and darker. The pubic hair in the male appears thin and less curly though possibly spread over a wider area than in younger years. The scrotum is longer and more flaccid and fails to contract on exposure to cold probably because of atrophy of the tunica dartos.



Fig. 226



Fig. 227

Fig. 226. Male aged 7 years. Loose ear, droopy eyelid, preauricular fold. Pigmented spot.

Fig. 227. Vermilion of lips has disappeared. Wrinkles cross lips.

In the female analogous regression of the labia majora takes place. The subcutaneous fat is often accumulated around the hips leaving the extremities and the chest relatively lean. The formation of the arcus senilis corneae begin.

Around 65 th hair growth in the ear, about the nostril and on the nape of the neck becomes more conspicuous in men as well as in women. The bristly hypertrichosis on the chin is often marked in the female sex.

At the age of 70 the facial wrinkles are often found crossing each other. Sometimes they form a netlike pattern or a papyraceous wrinkling like that seen in castrates. Senile pigmentations have increased. The skin is thin and a fold lifted from the back of the hand returns but slowly to the normal position. The head hair is usually thin or has disappeared. Complete senile baldness is occasionally seen in women also.



Fig. 213.—Female aged 80 years. All wrinkles are developed Drooping upper lid Yawning of the lips has disappeared



Fig. 230 Male aged 78 years Scalloped trophy of the skin



Fig. 20. Female aged 80 years. Senile keratoma basal cell epithelioma of nasolabial fold. Crow's feet wrinkles around the mouth. Vermilion border has disappeared.



Fig. 21. Male aged 88 years. The long ear of old age.

The thinning of the lips is completed at 75 so that hardly any vermillion can be seen. The thin mouth appears longer and sunken because of the atrophy of the alveolar ridges and the loss of the teeth. The backs of the hands are wrinkled like thin paper.



Fig. 248 — Male aged 72 years. Long teeth of old age.



Fig. 249 —Senile pigmented spot.

The eighties are characterized by the tired expression of the eyes caused by the drooping upper lid (senile ptosis). The radial wrinkles around the mouth are conspicuous. The cervical folds which appeared long before are very marked. The ears not only appear longer but are actually larger and flabby. The nose





Fig. 214.—Face to face view.



Fig. 215.—Profile hemangioma of the vermilion border.

seems to be larger. The skin of the back of the hands is now very yellowish thin and pigmented and the underlying fat has practically disappeared. The muscles have atrophied. The knuckles and small joints are very marked. There are not only transverse wrinkles but also longitudinal folds. The hand gives a bony impression.

It should be kept in mind that all signs of ageing are subject to relatively wide variations. However the evaluation of the appearance of wrinkles is a fairly reliable guide to objective age estimation.

Old age predisposes to a great number of *dermatoses*: Epitheliomas, keratosis, pigmented spots, small hemangiomas, especially the hemangioma of the vermillion border of the lips, xanthelasma of the eyelids, sebaceous adenomas, pendulous fibromas (acrochordon) and other neoplasms are common. The dryness of the skin caused by the reduction of the sebaceous glands is often troublesome. Pruritus senilis is another common and stubborn skin trouble of old age probably caused by the vascular changes. Purpura senilis (Bateman after Pasini<sup>140</sup>) is found on the acral and extensor surfaces. On slight trauma or even without it telangiectatic and purpuric spots appear and undergo the usual color changes leaving long lasting pigmentations. Such spots are often found on the back of the hands where the senile atrophy is pronounced and the exposure to slight trauma is greater than of other parts. Purpura senilis does not disturb the well being of the patient.

Thickening and opacity or dark discoloration of the toe nails is a common sight in old people. The rate of growth of the hair and of the nails is substantially reduced.<sup>141</sup>

<sup>140</sup>Pasini, A. Purpura Senilis, *Monatsh f prakt. Dermat* 62: 48, 1906.

## CHAPTER XXVIII

### METABOLIC DISORDERS

#### Diabetes

**The Blood Sugar Test**—With the increasing knowledge of diabetes, particularly with the development of the methods of blood sugar determination a large number of investigators have studied dermatoses in hyperglycemia as well as the presence of hyperglycemia in dermatoses. Today it is generally held that the absence of sugar in the urine does not rule out diabetes. The determination of the blood-sugar level after fasting and after a measured intake of sugar has become an important diagnostic procedure and many investigators have tried to correlate dermatoses and the blood sugar.

The normal fasting values given by different authors vary considerably but 80 to 120 mg. in 100 c.c. of blood may be considered normal. The gravimetric method (Bang, Hagedorn and Jensen) give lower values than the colorimetric method (Folin and Wu). Population with a diet rich in carbohydrates have a higher average blood sugar level than groups whose carbohydrate is lower.<sup>141</sup> For the determination of sugar tolerance some authors prefer the intravenous injection of glucose to the oral administration but today the drinking of 100 gram of dextrose in water after twelve hours of fasting and the determination of the blood sugar after one-half, one, two and three hours is a standard method.<sup>142</sup> It not only avoids the intravenous injection but duplicates the normal manner of sugar intake. It must be emphasized that disorders of the endocrine-sympathetic system, mensturation, exertion during the test and under- or overfeeding with carbohydrate during the days before the test may influence the blood sugar curve. Each considers a blood sugar tolerance curve characteristic for diabetes only if

- (1) The highest point of the curve is reached later than one-half hour after the ingestion of the sugar.
- (2) If the course of the curve is protracted enough to form a flat curve instead of the normal steep type.
- (3) If the fasting value has not been reached again within three hours.

Blotner<sup>143</sup> considers potential diabetes if the peak of the curve reaches 165 mg. per cent in one-half or one hour and he diagnoses diabetes when the blood sugar exceeds 170 mg. and some or all of the urine specimens contain sugar.

**Carbohydrate Metabolism in the Skin**—Ulrich and his collaborators designed a method of examining the skin sugar content which requires only a

<sup>141</sup>Urbach, E. Beiträge zu einer physiologischen und pathologischen Chemie der Haut. Inhibiert kutane Glykolytische als Ursache chronischer Dermatosen, *Sied. Klin.* 29: 236-240, 1933.

<sup>142</sup>Dieters, H. Glycemia und Diabetes Mellitus in *Selectes*, J. A. M. A. 331: 1109-1114, 1946.

very small quantity (30 to 40 mg) of skin taken with an electric biopsy punch of 3-5 mm <sup>1948 1949</sup>

The skin sugar content in laboratory animals varies considerably. In the rabbit it reaches 143 per cent of the blood sugar, the highest of the known values. The normal human fasting skin sugar amounts to only 58 per cent of the blood sugar <sup>1949</sup>. These findings are remarkable because the blood sugar levels in man and in laboratory animals do not differ greatly, both being between 83 to 111 mg per cent. These figures refer to the so-called free sugar. The bound sugar which can be obtained only by acid hydrolysis is fifteen times higher. The skin makes up 16 per cent of the body weight. Only the muscles weigh more of all the organs. Considering the high sugar content, together with the fact that the skin weighs one-sixth of the body and three times more than the liver, it is apparent that the skin is likely to be important in the sugar metabolism. Urbach <sup>1947</sup> considers a fasting skin sugar level of more than 68 mg per cent as pathologic. He showed that the curve obtained by skin sugar determinations after oral administration of 100 grams of dextrose imitates the blood sugar curve, but it requires about one-half hour more to reach the maximum and about one hour more to reach the fasting value again. Diet low in carbohydrate preceding the test causes a lower fasting level of the skin and blood sugar and a much higher maximum level of the skin and blood sugar curves than a high carbohydrate diet. A diet high in fat lowers the sugar content of the skin, while the blood sugar level remains the same. <sup>1949</sup> In the depancreatized dog the skin sugar increases much more than the blood sugar.

In diabetics the  $\frac{\text{skin sugar}}{\text{blood sugar}}$  ratio is high. Following the tolerance test the skin sugar is almost doubled and the time required for return to normal may be longer than five hours. <sup>1949</sup> This demonstrates that the diabetic skin stores sugar for a long time and would explain its often observed susceptibility to infections. Storage, decomposition and excretion of sugar seems to be a normal function of the skin. <sup>1949</sup>

Urbach found in diabetics with dermatoses such as furunculosis, hyderiditis, eczema, urticaria and pruritus the skin sugar higher (85 mg per cent) than in diabetics without dermatoses (66 mg per cent) in spite of about equal blood sugar levels. Thus in the diabetics with dermatoses the ratio  $\frac{\text{skin sugar}}{\text{blood sugar}}$  seems to be higher than in those without dermatoses. In animals

poisoned with extremely high doses of insulin the skin sugar never fell below a certain level. In diabetic patients, diet and insulin could not lower the skin sugar below 39 mg per cent. Pillsbury <sup>1949</sup> made the existence of an autonomous carbohydrate metabolism in the skin still more evident by studying lactic acid

<sup>1946</sup> Urbach & Van I. Der Zuckergehalt der normalen Haut, Biochem. Ztschr. 189: 474 1926.

<sup>1947</sup> Urbach, E. and Lentz, J. W. Carbohydrate Metabolism and the Skin, Arch. Dermat. & Syph. 72: 301-314, 1948.

<sup>1948</sup> Folio, O. Trimble H. C. and Newman, L. H. The Distribution and Recovery of Glucose Injected Into Animals, J. Biol. Chem. 75: 263-281 1927.

<sup>1949</sup> Pillsbury D. M. The Intrinsic Carbohydrate Metabolism of the Skin, J. A.M.A. 96: 430-432, 1931.

formation in the skin. He found this characteristic product of carbohydrate metabolism to be normally present. The skin contains several enzymes concerned with the splitting of carbohydrates. The stages of this process are the same as in the muscle and in the liver.<sup>1912</sup>

Urbach and his associates<sup>1917, 1919, 1924, 1927</sup> discovered what they called *isolated skin diabetes* or cutaneous glycolysis. They found that there exist in some cases a high fasting skin sugar and a flattened skin sugar tolerance curve in the presence of normal fasting blood sugar and a normal blood sugar tolerance curve. The patients suffered mostly from chronic eczema, furunculosis and vaginal or anal pruritus. A certain number of them responded well to insulin and a diet low in carbohydrates, clinically as well as in the fasting skin sugar and in the skin sugar tolerance curve. No transition of skin diabetes into frank diabetes has been observed.<sup>19</sup> This skin diabetes has not become widely known mainly because of the necessary punch biopsies and the new analytic method.



FIG. 21. Skin diabetes. Skin biopsy. (Urbach. From Urbach, H. *Skin Diabetes, Nutrition and Metabolism*. Grune & Stratton, Inc.)

Besides the excreted skin sweat and serum from artificial blisters have been studied with regard to their sugar content. Urbach emphasizes that the analysis of blister serum is no substitute for that of skin tissue. The blister serum sugar is higher than the skin sugar. Its changes after sugar ingestion are similar but

<sup>1912</sup>Kohlerwacht, J. Ueber den Kohlehydratstoffwechsel der Haut. *Deutsche med. Wchnschr.* 37: 1814-1815, 1912.

<sup>1913</sup>Mencorpe, C. Kohlehydratstoffwechsel und Haut. *Jahresb. f. Exalt. Fortbld.* 22: 27-36, 1931.

<sup>1917</sup>Urbach, E. Isoliert Glykolytische als Ursache krencher Furunkulose. *Zbl. B.* 44: 802, 1922.

<sup>1919</sup>Urbach, E., Depisch, F. and Picher, O. Isoliertes hohes Hautzucker bzw. Hautdiabetes. *Klin. Wchnschr.* 16: 432, 1937.

<sup>1927</sup>Urbach, E. Skin Diabetes. *J.A.M.A.* 129: 428-440, 1945.

slower than those of the blood sugar.<sup>1962,1922</sup> In persons who are intolerant to sugar the sweat contains an abnormal amount of sugar. After ingestion of much dextrose the sweat sugar may increase 100 to 150 per cent or more even 300 to 400 per cent.<sup>1900</sup> The sugar from evaporated sweat may accumulate on the skin and cause irritation pruritus and folliculitis just as the sugar does in persons who are occupationally in contact with sugar. Carrié and Koenig<sup>1900</sup> measured the sugar accumulated on the skin. It reaches its maximum four days after a bath the armpits collecting more sugar than open areas. The sugar on the skin is much higher in diabetics than in normal persons. The sweat sugar values determined by reduction only have been considered more recently as being much too high.<sup>1923</sup>

Another approach for testing the skin in diabetes has been advanced by Seelig.<sup>1921</sup> Using the method of McClure and Aldrich he compared the time which a wheel produced with .5 cc of 1 per cent aqueous glucose solution needed to disappear compared with one produced with 9 per cent saline solution. In diabetics and glucose wheels disappeared more quickly yet never before the controls with saline wheels. This seems to indicate an increased avidity of the diabetic skin for glucose.

The majority of the investigators tried to find out how the blood sugar influences the skin. The possibility that the skin or at least pathological changes of the skin might influence the blood sugar has been given much less attention.

Skin irritations of many kinds e.g. from croton oil<sup>1904</sup> injections of saline foreign proteins and olive oil increase the blood sugar within certain limits according to the intensity of the inflammation.<sup>1904,1908-1909</sup> The extract of artificially inflamed skin injected into normal rabbits raises the blood sugar level to a larger extent than extracts of normal skin. The increase is higher in rabbits with already inflamed skin than in rabbits with normal skin. It is interesting that high blood sugar curves in psoriasis may become normal after the skin symptoms have been cleared by local treatment.<sup>1909</sup> Marchionni and

<sup>1900</sup>Ferrari, A. V. Rilevanti fra il contenuto in glucosio del sangue del liquido di sudore dopo la somministrazione di zucchero per via orale ad individuali normali, *Dermosiflografo* 6: 202-214, 1921. X24. 201 763.

<sup>1901</sup>Marchionni, M. La sudore reattiva in alcuni dermoepatriti, *Arch. Ital. di dermat.* 47: 63-81, 1921. X24. 201 764.

<sup>1902</sup>Ueber, B. and Rabbinowitz, I. M. Excretion of Sugar in Sweat, *Arch. Dermat. & Syph.* 15: 705-712, 1927.

<sup>1903</sup>Carrié, C. and Koenig, B. Ueber den Zuckergehalt auf der Haut bei Normalen und Diabetikern, *Arch. f. Dermat. & Syph.* 378: 611-614, 1926.

<sup>1904</sup>Schulze, W. Sugar Content of Skin and Sweat. Comparative Study of Diabetic and Nondiabetic Subjects, *Arch. f. Dermat. & Syph.* 181: 471-483, 1940.

<sup>1905</sup>Worick, S. F. Diabetes Diagnosis, Intradermal Skin Tests, *Gay Hosp. Rep.* 68: 210-217, 1928.

<sup>1906</sup>Wasserman, L. Effect of Irradiation With Monochromatic Light on Blood Sugar and Lactic Acid in Rabbit, *Mechern. Ztschr.* 372: 284-286, 1924.

<sup>1907</sup>Ayton, H. J. Glucose Tolerance Reactions in Eczema, *Arch. Dermat. & Syph.* 11: 622-626, 1925.

<sup>1908</sup>Yamashita, A. Experimental Studies on Skin Sugar, *Jap. J. Dermat. & Urol.* 20: 113-1126, 1920. X21: 87 101. 1922. 638-652. 1923. 240-260. 1923. X21. 88 768. 42: 181. 43. 511.

<sup>1909</sup>Shizuka, I. Einfluss von Dermatitis-Haustextur auf Hautozucker, *Jap. J. Dermat. & Urol.* 21: 1308-1322, 1921. X21. 94: 203.

<sup>1910</sup>Marchionni, A. and Hoffmann, K. Ultravioletbestrahlung und Kohlehydratstoffwechsel, *Klin. Wchnschr.* 11: 1367-1373, 1933.

<sup>1911</sup>Manacopa, C. Bekkedal, R. H. and Schmid, R. Sugar and Glutathione Content of Skin, *Arch. f. Dermat. u. Syph.* 88: 67-78, 1922.

Hövelborn<sup>101</sup> studied the influence of ultraviolet light on the carbohydrate metabolism. At the height of the erythema the fasting value of the blood sugar drops and the blood pressure decreases. This together with the increase of blood diastase points to one or several insulin-resembling<sup>102</sup> substances in the skin produced either in the skin or in the pancreas on stimulation from the skin. Moncorps<sup>103</sup> also found a substance in the skin which raises the blood sugar.

**Incidence of Dermatoses in Large Groups of Diabetics.**—Greenwood<sup>104</sup> compared the skin of 500 diabetic and 500 nondiabetic general hospital patients. About 25 per cent of the diabetics either had or had had skin diseases: mainly pruritus (7 per cent), eczema, epidermophytosis, furunculosis and carbuncle (2 per cent) and xanthoma palpebrarum (18 per cent). The patients with a dry skin (20 per cent) seemed to be more apt to develop dermatoses than those with a moist skin. The figures were generally higher than in the nondiabetic group. The total percentages in the control group are meaningless because of the difficulty to obtain reliable figures for epidermophytosis. Tauber<sup>105</sup> found among 514 diabetics, most of whom were hospital patients, gangrene in 18 per cent, ulcers in 43 per cent, furuncles and carbuncles in 38 per cent, infected hands and feet in 23 per cent and pruritus vulvae et ani in 0.8 per cent. This and other lists show that the recorded incidences vary widely even in large groups, probably due to the selection of the studied series. Statistics of hospitalized diabetics are apt to carry a high percentage of severe complications, especially gangrene, which are much rarer in ambulatory groups (Lane's series given in Greenwood<sup>106</sup>).

How often is a dermatosis the presenting symptom of diabetes? Every experienced dermatologist will remember with satisfaction the cases of perioral eczema, balanitis or pruritus in which he first made the diagnosis of an underlying diabetes. In the large material of the Berlin University Skin Clinic 27 out of 1,000 patients were diabetics and only 13 per cent of them knew of their disease. In the others their diabetes was diagnosed by the dermatologist. Among the diabetic skin patients of the Berlin Clinic 59 per cent had eczema (one-fifth of these eczema of the genital region) and 22 per cent balanitis. These patients represent a group with uncontrolled diabetes.

The degree of control of the diabetes is probably the main factor which influences the incidence of dermatoses. The whole dermatological aspect of diabetes has changed since the introduction of insulin. In examining about 200 diabetic patients, most of whom were well controlled, the author was surprised to see how rare were even those skin diseases which are generally considered typical of diabetics. Epidermophytosis was seen to be neither more common nor more severe than in nondiabetics. Gangrene, furunculosis and carbuncle were rare, about 1 per cent. The most common skin change in the controlled diabetic is a slight yellow discoloration, probably due to minor degrees of carotenemia (*Xanthosis diabeticorum*).

<sup>101</sup>Greenwood, A. M. *Skin in Diabetes*. 200 Cases, J. A. M. A. 89: 774-778, 1927.

<sup>102</sup>Tauber, E. B. *Hyperglycemia in Diseases of the Skin*, Arch. Dermat. & Syph. 27: 195-201,

**Mycoses.**—Greenwood<sup>1970</sup> found epidermophytosis in 40 per cent of his series of 500 diabetics. Greenwood and Rockwood<sup>1970</sup> found clinical evidence of fungus infection in the interdigital spaces of the feet in 70 per cent of diabetic patients their diabetes being generally uncontrolled. All thickened and opaque



Fig. 247.—Epidermophytosis in diabetic patient.

nails were found to be infected. No relationship to the blood sugar level could be established. Percentages of other authors vary widely (see table in Gray and Close.<sup>1971</sup>) Because of the great differences in the incidence in normal control groups it is difficult to state whether the incidence in diabetics is actually higher than in comparable normal groups. Many authors<sup>19</sup> emphasize the importance of the nails as a source of reinfection.

The importance of *mycotic foot infections* in diabetics lies in the danger of more severe infections, complications and gangrene. The clinical aspect of epidermophytosis in diabetics does not seem to have special features.

Every dermatologist has seen in obese women the characteristic, though not very common picture of intertriginous genito-ingunal and inframammary dermatitis often caused by *monilia*. This bright red sharply bordered intertrigo surrounded by small pustular satellites is very suggestive of diabetes. Oral moniliasis (thrush) is common in infants but is rare in adults. If it occurs urine

<sup>1970</sup>Greenwood, A. H. and Rockwood, E. M. Skin in Diabetic Patients, Arch. Dermat. & Syph. 21 94-107, 1920.

<sup>1971</sup>Gray H. and Close W. E. Chirepody and Diabetes, M. Rev. 184 445-449, 1941.

<sup>19</sup>Kelly H. J. Significance of Dermatophytosis (Cause of Gangrene) Pennsylvania M. J. 21 431-444, 1923.





Fig. 21 Non-diabetic | tetracycline eruption infection of the groin



Fig. 2 Non-diabetic | Infantile acne eruption



Fig. 250. Inframammary nevi in obese diabetic woman aged 50 years



Fig. 251. —Xerosis in edigitalis in diabetic woman.

and blood should be examined for sugar.<sup>173</sup> Yeast infections of the hands, feet and particularly of the vulva occur mostly in uncontrolled diabetes.<sup>174</sup> Proper management of the diabetes without local treatment can control the infection. This indicates the specific influence of the diabetes.



Fig. 252 Monilia in diabetes (courtesy Division of Dermatology, Department of Medicine, University of Chicago.)

*Diabetic vulvovaginitis*: usually a mycotic infection.<sup>175-177</sup> It is encountered in about 50 per cent of women with diabetes. The vulva appears slightly swollen and tender, with a reddish blue color and a thin grayish surface. Abrasions and excoriations, together with a sensation of heat, cause much discomfort. The inflammation is usually limited to the moist surfaces, but may extend to the mons

<sup>173</sup>Christoph, *Poor and Diabetes*, Ed. 22, 808, 1927.

<sup>174</sup>Trant, H. F., Whit, L. and Humphill, R. B. Monilia of the Skin in Diabetes. *J. A. M. A.* 1921; 1290-1292, 1924.

<sup>175</sup>Himesline, H. C. Diabetic or Mycotic Vulvovaginitis. *J. A. M. A.* 190, 177-179, 1922.

<sup>176</sup>Himesline and Campbell. Diabetic or Mycotic Vulvovaginitis. *Am. J. Obst. & Gynec.* 85, 272-282, 1923.

venous, anus and crural folds. Small white areas (thrush spots) on the labia minora contain yeasts. Glucose applied in powder or solution is supposed to cause a flaring up of the vulvitis in mycotic infections as compared with vulvitis of other causes. Hesse<sup>1977</sup> speaks of mycotic vulvitis rather than of diabetic vulvitis, because it is not the irritation from the sugar-containing urine but the infection that causes the vulvitis. The sugar fermenting yeast, of course finds a good medium in the glucose-containing urine and tissues. Optimal growth of yeasts and also of staphylococci, is found on media with 150 to 200 mg per cent of sugar. This figure corresponds well to the sugar contents of serum in many diabetics.<sup>1978</sup>

Diabetes was the cause in 26 of 31 consecutive patients with pruritus vulvae.<sup>1979</sup> Fifteen of these 26 diabetics failed to show sugar in the urine. Only blood sugar tests and a detailed history established the diagnosis. These women were between thirty and fifty years of age. Such cases may often be treated as menopausal pruritus if no finer diagnostic test than the unreliable urine test is used.



Fig. 282.—Diabetic balanitis and sleeve of glass probe. (From Urbach, E. Skin Diseases, Nutrition and Metabolism, Grune & Stratton, Inc.)

Diabetic balanitis is much rarer than vulvitis the ratio being 1:3.<sup>1980</sup> It occurs less often in circumcised men whose glans penis is dry and does not give the yeasts such a favorable moist medium. Among 147 cases of diabetic balanitis treated in the University Skin Clinic in Berlin there was not one in a circumcised man.

Eczeema surrounding any not only the urethral and anal orifices is always suggestive of diabetes. Eczeema around the eyes may be caused by sugar-containing tears, perioral eczeema and perleche by sugar-containing saliva.

<sup>1977</sup>Engelhardt, W. Haben die beim Diabetiker gebilft auftretenden Infektionen durch Staphylokokken und Hefen ihre Ursache in dem erhöhten Haut- und Schweisszucker? *Diabetiker und Wechseljahre* 2037-2028, 1923

<sup>1978</sup>Balshofer, A. Hautkrankheiten und Diabetes mellitus. *Inaug. Diss. Berlin*, 1911

**Vascular Disease**—Vascular disease of slight degree is extremely frequent in elderly and middle aged diabetics. Abnormally low temperature, pallor or cyanosis of the feet have been observed in approximately one half of 124 patients.<sup>1071</sup> The capillary fragility of diabetics is demonstrated by the tourniquet test is greater at each decade than in nondiabetic groups.<sup>1072</sup> Gettson emphasizes the increased capillary reactivity in diabetes.

In many cases gangrene of the toe or foot can be traced to minor skin ailment like epidermophytosis, interdigital fissure, ingrown toe nail, infected corns and calluses and small injuries from self treatment.<sup>1073</sup> All these conditions should receive particular attention. Many of them are caused by improper and



FIG. 95. Diabetic gangrene.

tight shoes. Systematic foot hygiene in diabetics has been advocated by many physicians, having wide experience in the management of diabetes. The institution of special foot clinics in large centers has undoubtedly helped to decrease the number of serious complications.<sup>1074-76</sup>

<sup>1071</sup>Noble, M. Diabetes Mellitus as Observed in 100 Cases for 10 or More Years. Peripheral Vascular Findings in 88 of These Cases, *Am. J. Med. Sc.* 200: 23-24, 1943.

<sup>1072</sup>Beaver, F. B., Rudy, A., and Seligman, A. M. Capillary Fragility in Relation to Diabetes, Hypertension and Age, *Arch. Int. Med.* 73: 18-22, 1944.

<sup>1073</sup>Joslin, E. P. *Treatment of Diabetes*, Philadelphia, 1937, Lea & Febiger.

<sup>1074</sup>Brandelone, H., Standard, S., and Raffi, E. P. Prophylactic Foot Treatment, *Ann. Surg.* 106: 130-134, 1937.

In these foot clinics the patients are educated to follow a daily morning routine of a warm foot bath without or with little soap followed by an alcohol rub and dusting with boric acid foot powder. They are advised to massage their feet with lanolin at night. Epsom salt should not be used for the foot baths because it makes the skin dry. Commercial corn remedies should not be applied and blisters not opened. The toenails should be clipped properly. Foot exercises consisting of a series of movements of the toes, feet and legs are considered important if any vascular disease is present. All exercises are done six times and if there is a tendency to coldness the exercises should be done twice a day. An important part of the exercise is the alternating raising and hanging down of both legs for three minutes. Contrast baths of the feet are recommended. The patient should begin with 105° F (40.5°C) and change five times to 50° (10°C) keeping the feet one minute in each bath and finishing with the warm bath. He should keep his feet warm with stockings and not with hot water bottles. Expert care should be taken of abnormal toenails, calluses, corns and mycotic infections. Extremely well fitting shoes and comfortable stockings are important. No walking barefoot, no circular garters or bandages and no metal arch supporters are permitted.

*Impending gangrene* will usually be diagnosed by observing the following signs:—

1. The pulsation of the peripheral arteries, especially of the dorsalis pedis. Both sides must be compared. Good pulsation does not preclude gangrene of a toe because a more peripheral part of the artery may be occluded. Absence of pulsation does not always mean impending gangrene because a collateral circulation may develop.

2. If the color of the elevated and dependent extremity remains the same the prognosis is relatively good whether the pulse is palpable or not. Pallor on elevation, slow recoloring on return to horizontal position and purplish discoloration of the dependent extremities means extensive circulatory disturbance. The level of the abnormal discoloration indicates the approximate level of occlusion.

3. The skin temperature is taken with special thermometers or by running the hand (ulnar side) from the thigh to the toes. One should always compare both sides. A gradual fall of the temperature is normal but a sudden change is of the same significance as a level of discoloration.

4. The histamine test consists in scratching through a drop of histamine solution on both sides and on various levels or in intradermal injections. The wheal and flare formation is supposed to be in inverse proportion to the degree of circulatory impairment.

Diabetic gangrene does not occur in the lower extremities only and it is not entirely a disease of old age. Gangrene of many other parts of the body surface are on record. On the face gangrene may at first resemble erysipelas and later turn into a deep slough frequently with a fatal outcome particularly

## PLATE IV

1. Erythroid pigmentation of the hand (rings) when leucopur. Each corner pig on right thumb. Pig protrusion with silver-tipped hammer.

Necrobiosis (pyoderma diabeticorum) (E. Luck-Hagenbeim) (Courtesy Dr L. Babalian)

1. Diabetes - Infected (uninfected) site of stages of pyoderma.

4. Diabetes - three days later pyoderma seem localized.

5. Female, aged 21, as Xanthoma diabeticorum, small large lesion. Blood cholesterol 810 mg per cent.

6. Female, aged 21, as Xanthoma diabeticorum.



PLATE IV





if the cheek is involved.<sup>1966</sup> Loss of lips ears and particularly of the nose, as well as perforation of the septum and of the palate have often been reported. Gangrene of the penis of the vulva and<sup>1967</sup> of small and large superficial or deep areas of the skin are known. The superficial gangrene which occurs in small patches is called ecthyma. Though rarely diabetic gangrene may occur very early in life. Trauma plays a role in unusual sites of diabetic gangrene.

The treatment of diabetic gangrene is mainly a surgical problem. After drying of superficial necroses with subgallate of bismuth or other means the sores should be dressed with ointments containing as much cod liver oil as possible.

In every case of beginning or impending gangrene pancreatic extract (Pancreatic hormone Grant or Sharp and Dohme's pancreatic tissue extract) should be given a trial. One to 3 c.c. are given daily or on alternate days. Paudin another pancreatic enzyme-free preparation is given by injection and by mouth. Wolffe<sup>1968</sup> recently reported 100 cases of gangrene that had received treatment with enzyme-free pancreatic extract. Eighty-eight per cent of the beginning dry gangrene and sixty three per cent of the more severe cases with not more than two toes involved were healed. The majority of these cases were diabetics. The pancreas contains a vasodilatory substance which is able to neutralize the rise in blood pressure produced by epinephrine. It furthermore aids in fat metabolism by lowering the blood cholesterol and blood phosphatides. This substance is not identical with choline nor histamine. It may be identical or partly identical with the alcoholic, fat and insulin free neutral pancreatic extract, Lipocic,<sup>1969</sup> which lowers lipemia and allows depancreatized insulin treated dogs to survive for longer than two to three months without the feeding of fresh pancreas.

*Diabetic Ulcer*.—Trophic ulcer of the foot is not infrequently found associated with diabetes. The diabetic ulcer is not different in its appearance from other trophic foot ulcerations. It develops most often on the dorsum or the plantar surface of the big toe or at points of increased pressure. The patients are often overweight rarely young. Besides the care of the obesity exercises to improve the circulation and the topical application of cod liver oil are indicated. Well-fitting shoes and protection from cold are most important.

*Pruritus*.—Pruritus is, especially in women<sup>1970</sup> such a common diabetic dermatome that the urine should routinely be tested for sugar in all cases. In all stubborn and unexplained cases blood sugar tests should be done. More than fifty per cent of the cases of "pruritus sine materia" show patho-glycemic curves.<sup>1971</sup> Besides the dietary and insulin treatment French authors have

<sup>1966</sup>Stell, J. Diabetic Gangrene of Face. 2 Fatal Cases, J.A.M.A. 123: 1142, 1939

<sup>1967</sup>Ellis, C. W. W. Occurrence of Diabetic Gangrene in an Unusual Location, J.A.M.A. 123: 1182, 1939

<sup>1968</sup>Wolffe, J. D. Pancreatic Extract in Treatment of Gangrene, Am. J. Surg. 63: 108-116, 1939

<sup>1969</sup>Dreanetti, L. R. Van Prohaska, J. and Harms, H. P. Substance in Pancreas ( Fat Metabolizing Hormone) Which Permits Survival and Prevents Liver Changes in Depancreatized Dogs, Am. J. Physiol. 117: 173-181 1938

<sup>1970</sup>Campbell, G. Gordon. Relation of Sugar Intolerance to Diseases of the Skin, Brit. J. Dermat. 63: 297-304 1921



Fig 235 Urea diabetikum



Fig 236



Fig 237

Fig 236 Urea diabetikum

Fig 237 Same as after 4 weeks of diet and insulin treatment



Fig. 318. — Prion in uncontrolled diabetes



Fig. 319. — Pyoderma in uncontrolled diabetes

reported successful x ray therapy to the splanchnic areas.<sup>110</sup> Spleen extract too has been advocated. Pruritus has been observed not only in hyperglycemia but also in hypoglycemia.<sup>111</sup> Cuklberg and Hannidval treated such cases successfully with glucose injections and insulin.

Furuncles and Carbuncles have always been considered common in diabetes. This has been statistically confirmed by Greenwood<sup>112</sup> who found the incidence among 500 diabetics about twice as high as the general average of the hospital patient (2 per cent compared with 1.2 per cent) and 7 times higher when furuncles and carbuncles in the history were counted. Williams<sup>113</sup> who tried to prove that pyogenic infection are no more common in diabetes than in normals, showed that boils and carbuncles occur in 2.3 per cent of hospitalized diabetics. This figure is about four times the percentage of the general hospital average.

Tauber<sup>114</sup> who compared the incidence of furuncles and carbuncles in about 500 hospitalized cases of diabetes with the incidence in 500 patients with normal or rather low blood sugar levels found it to be twice as high among the latter. He also found a diet rich in carbohydrates (Wenckebach's diet), liver extract and daily intravenous injections of 500 c.c. of 5 per cent dextrose solution very helpful. Tauber's<sup>114</sup> figures have so far not been able to destroy the general and deeply rooted opinion that furunculosis is a frequent feature of uncontrolled diabetes.

**Stomatitis.**—Rudy and Cohen<sup>115</sup> examined the mouths of 403 diabetics, 138 of whom were edentulous. In uncontrolled diabetes particularly if oral hygiene is lacking heavy supra- and sub-gingival tartar deposits are often formed. Gingivitis swollen and bleeding gingival papillae and abscesses are common. The teeth which are often decayed become loose but should be saved. The dental condition improves if the diabetes is controlled. No surgical procedure should be done before control of the diabetes.

The tongue in uncontrolled diabetes is often dry and coated. The saliva has been found acid because of the high content of lactic acid. Thrush on the palate and pharynx often occur.

**Pruritus of the Meatus Acusticus** is sometimes very annoying and may cause recurrent furunculosis of the external ear.<sup>116, 117</sup>

<sup>110</sup>Gault, F. and Bismarck, A. Traitement des prurits diabétiques et des diabésides par la radiothérapie sympathique. Bull. Soc. franc. de derm. et syph. 38: 326-329, 1931.

<sup>111</sup>Dejars, J. Pruritus and Pruriginous Affections in Three Decades from Kohlschütter's Archiv. Actas dermatol. 29: 61-63, 1933. Zbl. 61: 76.

<sup>112</sup>Williams, J. R. Does Diabetes Mellitus Predispose the Patient to the Pyogenic Skin Infections? J. A. M. A. 818: 1257, 1912.

<sup>113</sup>Rudy, A. and Cohen, M. M. Diabetes Mellitus, Oral Aspects, New England J. Med. 219: 803-804, 1919.

<sup>114</sup>Mayer, H. H. Diabetes und Hals- Nerven- Ohrenkrankheiten, Wien klin. Wchschr. 58: 1841, 1892, 1927.

<sup>115</sup>Koch, R. and Minkels, H. Relation of Diabetes to Suppurative Conditions in Ear and Nose, Wien. klin. Wchschr. 90: 1241, 1243, 1926.

Miscellaneous—*Dupuytren's Contracture* of the palmar aponeurosis and Peyronie's disease (induratio penis plastica) either alone or together are rare but have a definite relationship to diabetes. Greenwood mentions the former having a percentage of 1.6 among his 500 diabetics. About twenty per cent of the patients with Peyronie's disease (induratio penis plastica) which often accompanies Dupuytren's contracture are diabetics. Nutritional deficiencies are reported to be more common in diabetes.<sup>1907</sup>



Fig. 260—Atrophy of subcutaneous fat caused by insulin injection. (From Ubach, E. *Skin Diseases, Nutrition and Metabolism*, Grune & Stratton, Inc.)

*Fat Atrophy*—A peculiar sequel of diabetes is the fat atrophy at the sites of injections of insulin.<sup>1900-1909</sup> which occurs in about 7 per cent of the cases.<sup>1900</sup> It is a harmless but sometimes disfiguring condition consisting of the localized loss of subcutaneous fat. There is a decided feeling of looseness or emptiness in the subcutaneous tissues. Several such pits the size of a silver dollar may coalesce. Young diabetics with increased basal metabolism are especially inclined to develop this unusual response to insulin. Shelly thinks that the insulin may cause a sudden release of glycogen from the muscle which helps to burn the fat.<sup>1900-1902</sup> Much rarer than fat atrophy is its opposite, lipoma formation following insulin injections.<sup>1904,1908</sup>

<sup>1907</sup>Gady, A. Unusual Case of Deficiency Disease in Patient With Diabetes Mellitus, *Endocrinology* 37: 206, 1949.

<sup>1908</sup>Polak, C. J. Fat Atrophy From Injection of Insulin, *J.A.M.A.* 87: 1846, 1926.

<sup>1909</sup>Depieck, F. Lokale Lipodystrophie bei langer Zeit mit Insulin behandelten Fäden von Diabetes, *Klin. Wchnsch.* 8: 1965, 1926.

<sup>1900</sup>Albert and Ferguson. Local Fat Atrophy After Insulin, *Endocrinology* 24: 741, 1929.

<sup>1901</sup>Shelly, J. A. Insulin Atrophy (of Fat Tissue), *Pennsylvania M. J.* 49: 347-349, 1927.

<sup>1902</sup>Winnett, E. B. Diabetes, 300 Cases, *J. Iowa M. Soc.* 29: 99-103, 1930.

<sup>1903</sup>Frel, W. Insulin Atrophy of Subcutaneous Fat, *Arch. Derm. & Syph.* 87: 524-525, 1928.

<sup>1904</sup>Barr, A. H. and Garrison, G. H. Lipodystrophy Atrophy and Tumefaction of Subcutaneous Tissue Due to Insulin Injections, *J.A.M.A.* 99: 16-18, 1932.

<sup>1905</sup>Odierstedt, X. Exkurskripte Hyperplasie des subcutanen Fettgewebes als lokale Folge von Insulin-Injektionen, *Endokrinologie* 10: 412, 1932.

The patient in hypoglycemic shock perspires freely or even excessively while the skin remains dry in diabetic coma.<sup>11904</sup>

*Xanthoma Diabeticorum*: a rare condition. Joslin<sup>11905</sup> observed only six cases among 1 000 cases of severe diabetes. The patients are mostly younger males. The xanthoma appears quite suddenly usually in large numbers on the extensor surfaces, the palm and the soles. The individual lesion is a small papule the size of a pinhead to that of a grain of wheat rarely larger, red in color with a yellow center which looks pustular but is xanthomatous. They often have in



FIG. 361. Female aged 21 years. Xanthoma diabeticorum (in color).

inflammation bases and itch moderately. The histology shows intra and extracellular deposits of fat with more inflammation and fibrosis than in primary xanthoma. Thannhauser and Magendanz<sup>11906</sup> classify the diabetic xanthoma with the secondary lipidoses which mean they are a complication of a lipemia which can be caused by diabetes as well as by pregnancy, icterus, nephritis or other conditions. The diabetic xanthoma respond to diet and insulin (see also chapter on lipidoses).

*Neurobiost. Lipolipica Diabeticorum* (Oppenheim (Rach)).—It is remarkable that a condition characteristic and not extremely rare dermatosis remained undescribed until 1929 when Oppenheim<sup>11907, 11908</sup> presented a case of a

<sup>11904</sup>Worth J. Common Acne and Insulin Hypoglycemia. *J. A. M. A.* 800: 973, 1927.

<sup>11905</sup>Thannhauser J. and Magendanz H. Differenzialdiagnose der Xanthomatösen Diseases. *22. Congr. A. I. Med.* 1862, 1746, 1917.

<sup>11906</sup>Oppenheim M. Eine noch nicht beschriebene Hauterkrankung bei Diabetes mellitus (Dermatitis xanthomatosa lipoides diabetica). *Wien klin. Wochenschr.* 48: 314-318, 1922.

<sup>11907</sup>Oppenheim M. Über eine bisher nicht beschriebene selbst eigige ähnliche Epithel-Depression der Epidermis und des Unterhautgewebes einschliessende chronische Dermatitis bei Diabetes mellitus (Dermitis atrophicans lipoides diabetica). *Arch. f. Derm.* Syph. 100: 876-893, 1922.

degenerative skin disease in a diabetic. Urbach<sup>304-305</sup> in presenting another case three years later emphasized the presence of lipid substances in necrobiotic foci. He related these findings with the disturbance of the fat metabolism in diabetes.

The lesions start as small red papules which grow slowly into irregular plaques from one to several inches in diameter. In their mature stage they are waxy or mottled with a red yellow center. The border is violaceous with a red or brown areola. Subcutaneous nodules may be covered with normal skin. The surface



Fig. 303 — Necrobiotic lipoidia diabetica (Urbach-Oppenheimer). From Urbach E. in *Diabetes, Nutrition and Metabolism*, Grune & Stratton, Inc.

of the older plaques is usually traversed by fine telangiectatic vessels. The plaques are quite hard especially along the edges. They are not elevated but the center of the lesions is flat or depressed. The surface of the older lesions is shiny as if covered with collodion. There is hardly any scaling. Ulceration of the center may occur. There is a tendency to heal slowly with an atrophic scar but this may take many years.

The average number of lesions runs from a few to a dozen. They are most often located on the lower legs. Lesions on the hands and in other regions have been described but none on the face. Itching or pain is never mentioned tenderness usually being the only complaint.

- <sup>304</sup>Urbach, E. Lipidstoffwechselkrankungen der Haut. *Handb. d. H. Gk.* 22: 225-274, 1923.  
<sup>305</sup>Urbach, E. Necrobiotic diabetes. Eine neue diabetische Stoffwechselkrankheit. *Ebd.* 61: 564, 1923.  
<sup>306</sup>Urbach, E. Eine neue diabetische Stoffwechselkrankheit. *Necrobiotic lipoidia diabetica*, *Arch. f. Dermat. Syph.* 106: 273-288, 1923.



The histology of necrobiosis lipoidica diabeticorum is of great interest. The primary phenomenon seems to be an intense localized angitis. There is an inflammatory thickening of the vascular wall which leads to gradual occlusion of the blood vessel particularly of the small arteries with slow necrosis of the areas involved. The collagenous fibers become waxy and swollen and the nuclei disappear or stain but poorly with eosin. The elastic fibers deteriorate. Hemosiderin is present explaining the brownish hue of the older lesions. The necrobiotic areas become impregnated with fat droplets which lie mostly but not



Fig. 462. Long-standing diabetes, obesity, hypertension, Behnke's disease-like rash.

always extracellularly, sometimes surrounding the vessels in a certain distance.<sup>291</sup> Lymph capillaries stuffed with fat have been demonstrated. The droplets stain bright orange red with Sudan III while the necrotic collagen is dull brown. Foam cells as in xanthomas, calcium deposits and giant cells have been observed<sup>292</sup> mainly in the periphery of older lesions.

<sup>291</sup>Gettler, B. Dermal Atrophicus Lipoides Diabeticus, *Med. Klin.* 31: 144, 190-192 1929.

<sup>292</sup>Nichols, L. Necrobiosis Lipoidica Diabeticorum With Xanthoma Cells (Case With Pulmonary Tuberculosis), *Arch. Dermat. & Syph.* 68: 606-611 1913.

Both neutral fats<sup>988</sup> and doubly refractory cholesterol have been demonstrated. High blood lipids especially cholesterol, have frequently been found. The fat in the necrobiotic tissues is probably deposited from the blood.

Ninety of the approximately one hundred cases so far presented were diabetics. There is a preponderance of the female sex.

The usual antidiabetic treatment does not seem to influence the condition but a diet low in fat as advocated in certain xanthomas has been recommended.<sup>989, 990</sup>

Diabetic carotenemia or *xanthosis diabetica* (see carotenemia) is probably the most common diabetic dermatome. It has long been considered harmless, and explained by the fat and vegetable diet of the patients. Recently Rabinowitch<sup>991</sup> found among 1014 diabetics fifty-nine cases of xanthosis, thirteen of whom had never been on special diets prior to the detection of this skin condition. The percentage of carotenemia in diabetics is probably much higher when the diagnosis is based on increased serum carotin and not only on clinical discoloration. Being a frequent accompaniment of severe diabetes, cardiovascular disease, insulin edema, resistance to insulin and hypercholesterolemia, it suggests an unfavorable prognosis for the diabetes. The disturbance of the lipid metabolism in diabetics, the failure to synthesize vitamin A from its precursor carotin, and possibly disturbed excretion of the carotin seem responsible for the accumulation of the lipochrome in the body.

### The Blood Sugar in Various Dermatoses

The blood sugar has been investigated in all common and many rare dermatoses. Except for the established diabetic dermatomes the results have been meager. In finding a high blood sugar level one should recall that inflammatory processes in the skin are able to raise the blood sugar.<sup>992</sup> The blood from capillaries of inflamed skin contains more sugar than from normal skin.<sup>993</sup>

In groups of eczema patients<sup>1994-1996, 997, 998</sup> a higher percentage of sugar intolerance has often been claimed but also denied.<sup>1999, 1000</sup> Dermatitis intertriginosa, seems more than other types of eczema correlated to sugar intolerance.<sup>999</sup>

<sup>988</sup>Zahler, E. P. and Caro, M. E. Necrobiotic Lipidosis Diabeticorum, Arch. Dermat. 80: 795-813, 1934.

<sup>989</sup>Green, F. and Macintosh, G. F. Necrobiotic Lipidosis Diabetica, Arch. Dermat. & Syph. 22: 491, 1933.

<sup>990</sup>Turback, E. Cutaneous Lipidosis, Dermat. Wochschr. 80: 371-380, 1933.

<sup>991</sup>Rabinowitch, L. M. Carotenemia and Diabetes, Canad. M. A. J. 28: 537-539, 1933.

<sup>992</sup>Urbach, W. Zur Blutzuckererhöhung der Dermatosen, Dermat. Wochschr. 84: 463-470, 1932.

<sup>993</sup>Widman, A. and Galla, A. Vergleichende Untersuchungen über den Zuckerspiegel in den Kapillaren pathologisch veränderter sowie normaler beschriebener Hauterkrankungen, Dermat. Wochschr. 34: 315-390, 1933.

<sup>994</sup>Allen, J. E. Hyperglycemia in Skin Diseases, South. M. J. 50: 732-742, 1937.

<sup>995</sup>Herrmann, E. H. and Hoyerzell, H. S. Histoecker und Hautkrankheiten, Med. Wochschr. v. Gessen 75: 2404-2420, 1931. Ed. 30: 370.

<sup>996</sup>Widman, A. and Galla, A. Abnormalities of Blood-Sugar Content in Eczema, Brit. J. Dermat. 37: 364-370, 1935.

Dry skin and "chapping" of the hand in cold weather should call attention to the possibility of a latent diabetes.<sup>122</sup> Chronic and unexplained eczema of the hand should be reason to search for diabetes.

It is an old experience that sugar and chocolate tend to make *acne* worse and that a diet low in sugar and starches is favorable for this condition. This is in accordance with Rosenfeld's<sup>123</sup> findings that sugar in the diet stimulates the secretion of the sebaceous glands more than fat. Schwartz<sup>124</sup> Highman and Malinkin found high blood sugar level in fifteen out of about thirty *acne* cases and also a similar percentage in seborrhea. Recently Semon and Herrmann<sup>125</sup> reported good result in treating *acne* with small doses of insulin.<sup>126</sup> They refer mainly to cases with menstrual exacerbations emphasizing that the blood sugar tolerance curve during menstruation is flattened reaching the fasting value more than three hours after the sugar intake. Many authors<sup>127, 128, 129</sup> more or less deny the relationship of *acne* and hyperglycemia. Lately healing of *acne* during hypoglycemic shock therapy of psychoses has been reported.<sup>130</sup> A great deal of evidence has been furnished demonstrating hyperglycemia in *psoriasis*.<sup>131</sup> Taulier was unable to confirm these findings. However there seems to be a relationship between diabetes and *psoriasis* which expresses itself in the occasional coincidence of both conditions in individuals and families. Greenwood<sup>132</sup> found 2.4 per cent of *psoriasis* among his 500 diabetics. This was ten times the percentage of the control group.

<sup>122</sup>Rose, C. A. Hyperglycemia and Skin Diseases, Brit. J. Dermat. & Syph. 51: 47, 1932.

<sup>123</sup>Rosenfeld, C. Hantala and Ditz. End. Gne. Met. N. 40, 1904.

<sup>124</sup>Schwartz, H. J. Highman, W. J. and Malinkin, H. C. Sugar Content of the Blood in Various Diseases of the Skin. J. Cut. Dis. 31: 129-153, 1915.

<sup>125</sup>Semon, G. Dermatology in Diabetes, Dermatologica 57: 69-92, 1943.

<sup>126</sup>Strickler, A. and Adams, P. D. Blood Sugar Metabolism in Certain Dermatoses, Especially in *Acne Vulgaris*. Arch. Dermat. & Syph. 28: 1-10, 1932.

## CHAPTER XXIX METABOLIC DISORDERS

### Lipidoses

**Chemical Data.**—The following lipids occur in the organism

1 *Sterols* This important group which includes cholesterol and its esters the bile acids the sex hormones and some other organic substances has a characteristic structure with four rings.<sup>1929</sup> Cholesterol is absorbed and synthesized in the body. It is excreted in the bile and partly reabsorbed the larger part being transformed into coprosterol and eliminated with the stools. Cholesterol always accompanies neutral fat.

2. Nitrogen and phosphorus-containing *phosphatides* such as lecithine cephalin sphingomyelin and the cerebroside.

3. The *neutral fats fatty acids and soaps*. These form the bulk of the body fat.

Normal (average) values for lipids in the blood serum <sup>1930</sup>

	mg% Plasma		mg% Of total lipids
Total cholesterol	180	(110-150 Windana) (100-210 Peters and Van Dyke)	34
Cholesterol esters	125	(40-70)	70
Lecithin	225		43
Total fatty acids	345	(190-420) (Peters and Van Dyke)	66
Total lipids	525	(700-800 Schaefer <sup>1931</sup> ) (570-820 Peters and Van Dyke)	100

Three per cent of the net weight of normal skin is made up of lipids. Five to fifteen per cent of the total lipids is cholesterol. Lecithin varies from only a trace up to 30 per cent of the total lipids.

The lipids in the serum depend on the intake and absorption the migration the deposition and disintegration of fat in the system and on the disturbances of the lipid metabolism in the cell.<sup>1930</sup>

**Pathology and Pathogenesis.**—Several disturbances of the fat metabolism are accompanied by tumor-like lesions in the skin and in other organs which are called *xanthomas*. While there are vast differences in the clinical appearance and in the severeness of the systemic involvement the histologic picture of all xanthomas is characterized by the presence of certain characteristic cells which are imbedded in a stroma.

<sup>1929</sup>Thakshammer S. J. *Lipidoses*, Oxford Medicine, Vol. IV VIIA, New York, 1940, Oxford University Press

<sup>1930</sup>Montgomery H., and Ostberg, A. E. *Xanthomatosis*, Arch. Dermat. & Syph. 37: 373-402, 1934

These cells called foam cells are large at least of epithelium size. They occur mostly in nests but diffuse infiltration to the degree of almost complete substitution of the normal tissue is known. The foam cells are constituent of the reticulo-endothelial system (Aschoff and his school see Thannhauser<sup>1921</sup>). Periadventitial reticulum and phagocytic connective tissue cells may become foam cells by being stuffed with fat droplets. In their mature stage they look alike. The foam cells may form giant cells of various types but there are no mitoses. Pigment probably of blood origin is frequently present. Cholesterol esters stain brown with Sudan III and dark blue with Nile blue sulfate. In polarized light they show the cross figures of double refraction.

The conceptions of the pathogenesis of the xanthoma and especially of the origin of the lipid in the foam cells have often changed.<sup>1919, 1921, 1921</sup> Pollitzer and Wile<sup>1921</sup> observed that the xanthomatous changes started in the adventitia of the small blood vessel. They concluded that the lipid substances in the xanthoma cell stemmed from extravasated blood and that their presence stimulated the connective tissue of the skin to hyperplastic growth. L. Pick and Linku<sup>1922</sup> however refuted the idea of hyperplasia or tumor formation. They suggested that the cholesterol infiltration of the cell was caused by the hypercholesterolemia which is often associated with xanthoma formation. However xanthoma cases without hypercholesterolemia and the frequent hypercholesterolemia in diabetes, icterus, renal disease and pregnancy without xanthoma formation made it probable that hypercholesterolemia was not the only source of the fat in the foam cells. Aschoff and his school (lit see Thannhauser<sup>1921</sup>) demonstrated that *only the cells of the reticulo-endothelial system could become xanthoma cells*. Another advance was the *chemical identification of the lipids in the various forms of lipidoses with cholesterol dominating in the xanthomas*.<sup>1922</sup> L. Pick<sup>1922</sup> interpreted xanthoma formation as a "storage disease". The fat droplets which were taken up and stored like vital dyes by the cells of the reticulo-endothelial system apparently could not be disintegrated in the intermediary metabolism.

The decomposition of the blood lipid in the light of colloid chemistry is the center of the xanthoma theory of Bloch, Schaaf and Werner.<sup>1924, 1925</sup> propounded later especially by Schaaf.<sup>1926</sup>

These authors emphasized the importance of the *ratio of the lipid constituents in the blood and in the tissues* (free and bound cholesterol phosphatides, true fats and perhaps other compounds as well). A change of the ratio of the lipid fractions would disturb the equilibrium of the lipid emulsion of the serum and lead to a coarsening of the lipid particles in the emulsion to decomposition and

<sup>1919</sup> Pollitzer A. and Wile L. Xanthoma Tuberosum Multiplex, J. Cutan. Dis. 39: 225-241, 1912.

<sup>1921</sup> Pick L. and Linku F. Ueber doppelthermoide Substanzen in Harn, Serum, et Mesenterie. Prakt. Dermat. 8: 46, 1920.

<sup>1922</sup> Pick L. Classification of Diseases of Lipid Metabolism and Gaucher's Disease. Am. J. M. Sc. 125: 453-480, 1922.

<sup>1924</sup> Bloch, B. Metabolism, Endocrine Gland and Skin Diseases. Special Reference to Acne Vulgaris and Xanthoma. Brit. J. Dermat. 43: 61, 1921.

<sup>1925</sup> Schaaf, F. and Werner A. J. Die Pathogenese der Xanthome. Die Beziehungen von Cholesterin-Phosphatid- und Gesamtstoffgehalt des Blutes zur Entstehung der Xanthome. Arch. f. Dermat. 162: 217-229, 1920.

precipitation of individual constituents in the tissues and finally to xanthomatous lesions. It was suggested<sup>190</sup> that the regulation of the concentration of fat emulsifying agents is a particular liver function the disturbance of which causes an impairment of the colloidal dispersion of fats in the blood serum and an increased tendency to throw the fats out of the emulsion. Local contributory factors may modify the distribution of the xanthomas which develop in reaction to the deposits of de-emulsified fats. After formation of xanthomas the metabolic disturbance may subside leaving the xanthomas. In such cases xanthomas without symptoms of disturbed fat metabolism may be encountered.

Schaaf's conception was based on Spranger's<sup>189</sup> investigations of emulsions. A fat in water emulsion is stable only if the concentrations of emulsifying agents are present in a definite ratio to each other. Only under these optimal conditions can the fat droplets remain in the finest possible state of dispersion. Every variation in this ratio increases the readiness with which the fat separates from the water. Cholesterol, cholesterol esters and the phosphatides play an important role in the emulsification of fat in water. In Ringer's solution containing proteins in quantities corresponding to those in the blood serum optimal distribution of neutral fat in the presence of cholesterol and cholesterol esters takes place only if this mixture of emulsifying agents contains 60 per cent cholesterol esters. In normal blood serum 60 to 70 per cent of the total cholesterol is present in the form of cholesterol esters. This fact stands in striking agreement with the optimal concentration of these two emulsifying agents.

The ratio may also be changed by local factors such as trauma and inflammation. Schaaf's conception of xanthoma formation is further based on the experimental production of xanthomas in animals. Xanthoma formation in patients with a normal total fat content or a normal total-cholesterol content is explained by the assumption of an abnormal ratio between the emulsifying agents especially cholesterol and cholesterol esters, phosphatids, neutral fats and fatty acids. The absence of xanthomas in hyperlipemia or hypercholesterolemia can be explained by the stability of the colloidal system in spite of the total increase of lipids due to the correct ratio of the constituents.

Montgomery<sup>191</sup> recently reemphasized the old experience that cutaneous xanthomas are not uncommonly seen in association with hepatic disease especially obstructive jaundice. (See Xanthomas.)

Thannhauser and Magendanz<sup>192</sup> and Thannhauser<sup>193</sup> emphasized and proved again with a great array of evidence both chemical and clinical that the specific lipids which form the cellular deposits are only in some cases present in excessive amounts in the blood serum. They claimed that there is no proof of a colloidal decomposition of the serum or of the cell fluids resulting in precipitation which was the prerequisite of the hypothesis.

They concluded that in one group of lipidoses which they called primary lipidoses the cause must be an intracellular disturbance of the lipid metabolism. The fat droplets in the cells are in their opinion not supplied by the

<sup>189</sup>Spranger, W. *Zur physikalischen Chemie der Körperfett. Ein Beitrag zur Physiologie der Verdauung.* Hochbr. Kocher 206 161-178, 1929.

<sup>191</sup>Montgomery H. *Xanthomasides, J. Invest. Dermat.* 2 322-351 1929.

blood stream but formed and retained within the cell in the presence or absence of hyperlipemia. This theory found important support in the observation that *tissue cultures of xanthomas* are able to develop doubly refractile substances.<sup>291</sup> The primary lipoidoses are often hereditary. Thannhauser and Magendanz<sup>292</sup> did not deny that hyperlipemia may cause xanthoma. Xanthomas in hyperlipemia of which the diabetic xanthoma is the best known type were grouped together as secondary or hyperlipemic xanthomatoses.

### Xanthoma

The cutaneous xanthomas are either solitary, localized in a few areas or scattered over the body surface. The solitary xanthoma is represented mainly by the eyelid xanthoma (xanthelasma) which is almost always flat (Xanthoma planum). Xanthomas in other regions are usually prominent either papular or tuberous (Xanthoma tuberosum multiplex). The xanthomas which are scattered over the body are mainly discrete shotty papules (Xanthoma disseminatum) which sometimes form large tuberous plaques.

Xanthoma planum palpebrarum (often called xanthelasma) is the only common type of xanthoma. All the others are rare conditions. It forms a single or more often a small number of oblong soft flat hardly prominent light yellow plaques. They surround the inner canthus in an arc which extends in the upper and lower lid. Rare atypical lesions may be red, brown or white, hard or tuberous. The author saw a case of xanthoma palpebrarum with tuberous nodules the size of a hazelnut so that the vision became disturbed.

The lid xanthoma appears mostly in the fifth and sixth decades.

The common and reputedly harmless but popularly and medically suspected xanthoma palpebrarum did not prove so insignificant as often believed. Montgomery<sup>293</sup> studied 38 cases. More than 20 per cent had serious cardiovascular disease, hypertension, coronary sclerosis or angina pectoris. There was a definite increase in one or more of the blood lipids<sup>294</sup> and a consistent increase in lecithin. Montgomery<sup>295</sup> concluded that xanthoma palpebrarum is an accompaniment of systemic disease and that the condition is simply a variation of one of the types of xanthoma. Polano<sup>296</sup> found high or otherwise abnormal blood lipids in 25 per cent of the eyelid xanthomas. Thannhauser and Magendanz<sup>297</sup> call "forme fruste" of essential xanthomatosis a condition in which slight xanthoma of the lids, dark pigmentation around the eyes and xanthomas of the skin due to carotenemia are the only (and inconstant) heraldromes. However, there is a high blood cholesterol and a low basal metabolism. Diabetes and signs of angina pectoris are not infrequent findings. The incidence of eyelid xanthomas in middle aged lepers (10 per cent) is more than ten times higher than normal. It can be explained by high blood cholesterol and leprosy involvement of the liver which is encountered in almost all necropsies.

<sup>291</sup>Biedermann, W. and Hofer, K. K $\ddot{u}$ chtigung von xanthom $\ddot{a}$ hnlichem Xanthomgewebe *in vitro*. Arch. f. exper. Zellforsch. 10: 83, 1930.

<sup>292</sup>Curtis, A. H. and Berger, J. P. Effect of Feeding Lipotropic Substance to Patients With Xanthelasma. Arch. Dermat. & Syph. 53: 252-256, 1913.

<sup>293</sup>Polano, M. H. Die Xanthomatosen der Haut. Arch. f. Dermat. & Syph. 161: 129-172, 1940.



Fig. 264



Fig. 265

Fig. 266



Fig. 267

Fig. 264.—Xanthoma tuberosum multiplex. Severe disseminated papules. (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)

Figs. 265-267.—Xanthoma. (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)



**Xanthoma Tuberosum Multiplex and Xanthoma Diseminatum**—A tendency to form lines, stripes or oblong arrangement is a peculiarity of both the xanthoma palpebrarum and the disseminated types.<sup>200</sup> *Multiple xanthomas in small numbers (xanthoma tuberosum)* are typically localized on the extensor surfaces of the elbows, the knees and the heels. These xanthomas except those of the palm are rarely as flat as those of the eyelid. Papular, tuberos or lobulated form on flat bases or short peduncles occur. The individual xanthomas may be crowded in ridges or furrowed plaques which may cover an entire axilla.<sup>201</sup> The xanthoma in the neighborhood of joints and tendons may be very firm, originating in the tendons or tendon sheaths and may become adherent to the bones. The variety of features and the transitional types show that a sharp anatomical distinction between localized and multiple and also between flat and tuberos xanthomas is not possible.



Fig. 26. *Xanthoma tuberosum multiplex*. Courtesy Division of Dermatology, Department of Medicine I (West) of Chicago.

Montgomery studied 26 cases of *xanthoma tuberosum*. High blood cholesterol, familial histories and early coronary (27 per cent) or other forms of severe vascular disease (46 per cent) were though not constant surprisingly frequent features. The combination of xanthoma tuberosum of the extensor surfaces with occlusive arterial disease is known since at least 1873 (Fugge after Thannhauser<sup>202</sup> also Barker<sup>203</sup>).

<sup>200</sup>Wise F. and Garb, J. Xanthoma Diseminatum With Unusual Form of Eruption, Arch. Dermat. & Syph. 45: 733-735 1942.

<sup>201</sup>Barker W. Occlusive Arterial Disease of Lower Extremities Associated With Lipemia and Xanthoma Tuberosum, Ann. Int. Med. 12: 1891-1899.

The rare *disseminate xanthoma* is characterized by an abundance of small papular shotty lesions and plaques. This type favors the flexor surfaces, but may involve the entire skin. Involvement of the sclerae and of the upper air passages occurs.



FIG. 309.—Xanthoma tuberosum multiplex. (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)

Herrmann and Nathan<sup>100</sup> described very thoroughly (1926) two cases of xanthomatosis. In one case small xanthomas were disseminated over the whole body surface and the blood cholesterol was normal. In the other case the

<sup>100</sup>Herrmann, F. and Nathan, F. Zur Frage der Xanthomatose. Arch. f. Dermat. u. Syph. 123: 573-601, 1926.



Fig 270.—Four siblings affected with hyper-xanthoma on the extensor type. Father who had high blood cholesterol married second cousin. Of nine children, five were xanthomatous. One of the other children suffered from cardiac disease and had like another non-xanthomatous child, high blood cholesterol. (From Bloom, D. Kaufman, R. R. and Stevens, R. A. Arch. Dermat. & Syph. 1942.)

xanthomas were tuberous and limited to the extensor surfaces of the knees and elbows, to the extensor tendons of the fingers and to both Achilles tendons. The blood cholesterol was high a brother of the patient had hypercholesterolemia without xanthomas. The authors emphasized that the two cases represented *two clinically and pathogenetically different types of xanthomatosis*.

More recently Polano<sup>234</sup> Thannhauser and Magendanz<sup>235</sup> Montgomery and Osterberg<sup>236</sup> and other writers investigated the features of the two types. Tuberous xanthomas of the extensor surfaces in moderate number appearing early in life involvement of the tendons and tendon sheaths cardiovascular and liver disease, high blood lipids and dominant heredity characterize one type. Disseminate abundant small nodular xanthomas with predilection for the flexor surfaces involvement of the brain and nerve tissue causing diabetes in adiposis and invasion of the bones larynx lungs and lymph nodes feature the

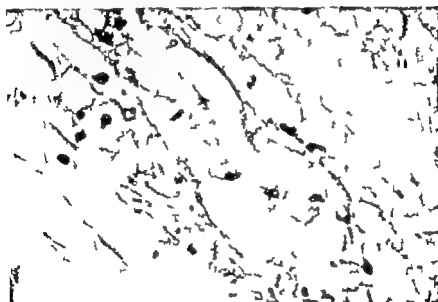


FIG. 271.—Hereditary xanthomatosis. Foam cells in lipid deposit in the aorta. (From Bloom, H. Kaufman, S. B. Stevens, R. A. Arch. Dermat. & Syph. 10:12.)

other type. There is no jaundice. These cases of the disseminate type usually have normal or high normal blood-cholesterol. The prognosis is particularly bad if the air passages are involved which may necessitate tracheotomy. Thannhauser and Magendanz<sup>235</sup> emphasize that they were not able to find a single case described in which disseminate xanthoma was found combined with endocardial and vascular xanthoma. The situation is quite different in the extensor type. The xanthomatous involvement of the endocardium the valves and the large vessels particularly the aorta is the cause of the sudden deaths which occur very strikingly in the xanthoma families. The case of Arning is particularly well known. The mother and five out of nine children had xanthomas. Three of

the children died at the ages of 16, 21 and 26 years of sudden heart attacks, two of them while dancing. Similar dramatic fatalities have been reported repeatedly.<sup>244</sup> The exhaustive necropsy findings in such a case have recently been published by Siegmund.<sup>245</sup> A girl of six years had been showing xanthomata tuberosa of the extensor surfaces of the buttocks and of the eyelids since the age of six months. Gradually the girl grew weaker and died from circulatory collapse. The heart valves, the root of the aorta and the coronary arteries showed lemon yellow xanthomas with cholesterol and calcium deposit. There was central congestion and atrophy of the liver, but the Kupffer cells were free of fat. The kidneys showed xanthoma in the papilla. It is remarkable that the reticulo-endothelial system was free of fat. Two years later a brother 11 years old died suddenly. The post mortem findings were almost identical and so were those in one of the 5 tainted siblings in the case of Bloom, Kaufman and Steven.<sup>246</sup>

*Liver disease* was found connected with xanthoma as early as 1850 by Addison and Cull.<sup>247</sup> Montgomery<sup>248</sup> demonstrated hepatic disease, particularly obstructive jaundice, in 8 out of 55 xanthoma cases. Xanthomatosis in icterus following neopraphenamine treatment has been seen in several instances.<sup>249, 250</sup> Biliary cirrhosis is apt to be seen with cutaneous xanthomas of the flexor surfaces. The cause of the obstructive jaundice is often found in xanthomatous changes of the bile duct.<sup>251</sup>

*Hyperlipemia* is present in tuberosus xanthoma but the normal ratio between cholesterol and cholesterol esters frequently remains undisturbed. It inversion proves severe liver damage.<sup>252</sup> Phosphatides (lecithin) are likely to occur. In many cases of hepatic disease associated with cutaneous xanthoma in other location than in the eyelids, *palmar* lesions can be found. The eyelid xanthomas in jaundiced patient often look lighter than the neighboring skin.

Cutaneous xanthomas may undergo involution as the condition of the liver improves. Thannhauser and Magendanz<sup>253</sup> point out that frequently the cause of the liver disease in tuberosus xanthoma is a *xanthomatous biliary cirrhosis*. Enlarged liver and spleen with jaundice of years duration, hypercholesteremia with inversion of cholesterol/cholesterol esters, together with xanthomata tuberosa and plana of the extensor surfaces and buttocks are a characteristic triad. If xanthomas of the tendon sheath and tuberosus xanthomas of the skin exist over a long time without jaundice, involvement of the liver is rare.

In cases of biliary cirrhosis caused by xanthomatous involvement of the liver an *eruptive, universal papulopustular form of xanthoma* was seen, which in con-

<sup>244</sup>Bloom, D., Kaufman, H. R. and Steven, H. A. Hereditary Xanthomatosis: Familial Incidence of Xanthoma Tuberosum With Hypercholesterolemia and Cardiovascular Involvement. Sudden Death in Several Cases. Arch. Dermat. & Syph. 48: 118, 1942.

<sup>245</sup>Siegmund, H. Kardiovaskuläre Xanthomatose als Todesursache bei Jugendlichen, Mischchen med. Wchnsch. 85: 1617-1619, 1938.

<sup>246</sup>Addison and Cull. On certain Affection of the Skin. Viscidities (1) Plana, (2) Tuberosa, Guy's Hosp. Rep. 2nd Series, vol. 7, p. 265, 1851.

<sup>247</sup>Kaichar and Stokes. Multiple Xanthomas. Arch. Dermat. & Syph. 27: 122, 247, 1923.

<sup>248</sup>Vahl O. Formen der generalisierten Xanthomatose. Dermat. Wchnsch. 24: 577-583, 1923.

trast to xanthoma without liver involvement was extremely itchy. The soft small papules were scratched so that a prurigo-like picture resulted.

The multiple forms have been encountered early in life in many cases in childhood. Urbach emphasizes that in childhood the fresh papular lesions are often bright red and not yellow due to the more abundant vascularization of the infantile skin. The xanthomas rarely heal spontaneously.

**Hand-Schüller-Christian's Disease** is a syndrome related to the xanthomatoses. It is characterized by the triad: defects in the flat bones of the skull, exophthalmus and diabetes insipidus.<sup>294a</sup> Rowland<sup>295a</sup> recognized the lesions of this disease as a special type of xanthomatosis with lipid storage in many parts of the reticulo-endothelial system. The infrequent involvement of the skin is surprising in this syndrome in view of the particular affinity for the skin in the other forms of xanthomatosis. There are on record some cases with eczematous or purpuric, yellow or red-brown widespread papular rashes. A few developed xanthomata palpebrarum and disseminata. In one of the cases<sup>296a</sup> the lenticular dermal xanthomas occurred in great profusion about the mouth and neck and the flexures of the big joints. On the penis they were so numerous that a phimosis resulted. Purpura may precede the xanthomas. In the eczematous lesions of one case foam cells were found.<sup>297a</sup> Gottron<sup>298a</sup> interprets the Hand-Schüller-Christian dermatosis as a primary granulomatosis with secondary lipid deposits in the later stages. This closely follows the conception of Chester<sup>299a</sup> who considered the granulomatous changes as the primary trouble and the lipid infiltration as secondary in the disorder. Hypercholesterolemia has often been found.

**Secondary Xanthoma**—(Xanthoma diabeticorum etc.) Thannhauser and Magendanz<sup>300a</sup> emphasize that the eruptive form of xanthoma (xanthoma diabeticorum) is etiologically entirely different from all xanthomas due to primary xanthomatosis. It is a symptom of lipemia and may occur in diabetic lipemia as well as in lipemia associated with other diseases. It has been observed in cholesterolemia due to icterus, pregnancy or nephritis. The difference between primary and secondary xanthoma is well illustrated by the rare cases of combination of both. In these cases the eruptive lesions disappeared under dietary treatment but the tuberous primary xanthomata remained.

The eruptive sub-acute transitory and inflammatory character is the main distinguishing feature of the secondary xanthomas of which *xanthoma diabeticorum* is the best known (see diabetes).

**Treatment of Lipidosis**—According to Thannhauser and others the normocholesterolemic type does not respond to dietary treatment. The cases

<sup>294a</sup>Christian, H. A. Defects in Membranous Bones, Exophthalmos and Diabetes Insipidus. *Contributions Medical and Biological Research*, vol. I, New York, 1919. Paul B. Hoeber, Inc. p. 390.

<sup>295a</sup>Rowland, B. S. *Christian's Syndrome and Lipoid Cell Hyperplasia of the Reticulo-Endothelial System*. *Ann. Int. Med.* 2: 1577-1599, 1929.

<sup>296a</sup>Gottron, H. Schüller-Christian Syndrome. *Arch. f. Dermat. u. Syph.* 1921; 801-731, 1912.

<sup>297a</sup>Wagner, E. Die Speicherkrankheiten (Thesaurismosen). *Ergebn. d. inn. Med.* Karger's 22: 246, 1927.

<sup>298a</sup>Chester, W. Ueber Lipidgranulomatose. *Virchow Arch. B. path. Anat.* 279: 501-602, 1930.

associated with hypercholesterolemia may respond to a diet low in cholesterol. Such a diet is mainly vegetarian, no animal fats being permitted.

Lipocafe is a defatted alcoholic pancreatic extract studied by L. R. Dragstedt. It seems to contain a hormone which influences high lipid values in the blood and it should be tried in hypercholesterolemic xanthomatosis.

Diabetic xanthoma respond quite readily to diet and insulin. The diet should avoid too much fat, particularly animal fat.

A trial should be given to the treatment of xanthomatosis with ultraviolet rays. The effects seem to be of a general nature exceeding the radiated area.<sup>2964</sup> X-ray treatment is locally effective in the tumors of Hand-Schüller-Christian's disease rarely in other xanthoma. The eyelid xanthomas may be treated locally.

A few very rare diseases which are interpreted as lipidoses may be mentioned briefly.



Fig. 272. Lipoidosis cutis et mucosae (lipid proteinosis) (Urbach-Wiethe). (Courtesy Dr. Erich Urbach.)

**Extracellular Cholesterinosis (Kerl Urbach).**—This is a chronic disease coming on over many years. Maculopapular coalescent violaceous indistinct lesions and disseminated yellowish nodules are seen on the trunk. In addition there are tuberous tumor like hard scaly larger nodules on the extensor surfaces of the arms and hands. Some nodules appear on the soft palate.

<sup>2964</sup>Lehmann, St. Xanthoma diabeticorum behandelt mit Quarzlicht. *DM.* 22: 26-27 1937.

The fresh lesions are transparent papules with central vesicles. Spontaneous involution occurs frequently. The spleen is large and hard. Serum cholesterol may be abnormal.<sup>200</sup> The lesions contained five times the cholesterol of the



Fig. 372.—Lipoidotic crisis as macroses (Urbach-Wiethe). (From Ramos Silva, J. Arch. Dermat. & Syph., 1942.)

normal skin. Histological examination revealed an enormous extracellular lipid infiltration (mainly with cholesterol) and destruction of the elastic fibers. Even the apparently normal skin showed lipid infiltration of the vascular walls. Montgomery<sup>2027</sup> after describing a similar case does not feel that the recognition of a new entity is justified. In contrast to Urbach's findings foam cells were present.

X-ray treatment was successful in a case of Frost and Anderson.<sup>2008</sup>

<sup>2008</sup>Frost, K. and Anderson, O. R. Extracellular Cholesterol of Urbach. Arch. Dermat. & Syph. 53: 1061, 1929.



**Lipoidosis cutis et mucosae (Lipid Proteinosi) (Urbach-Wiethe)**<sup>294</sup>  
 This condition has been shown to be a definite clinical and especially histological and histochemical entity.<sup>297,298,299</sup> About thirty cases have been published showing a surprisingly uniform syndrome. The disease affects the skin and the mucosa in all the reported cases with nodular or hyperkeratotic lesions. Hoarseness in the first years of life is a characteristic early sign. A somewhat varicoidform eruption appears during infancy and leaves irregularly outlined soft depressed scars. The hair growth is sparse. Later there is brown pigmentation and a scattering of yellowish very small papules on the face, the nape of the neck and the dorsa of the hand. The papules are not follicular.<sup>300</sup>



Fig. 274. Lipoidosis cutis et mucosae (Urbach-Wiethe). From Ransom: 301. J. Arch. Dermat. & Syph. 1942.

Irregular scarry ridges and patchy depression give the face a characteristic knitted appearance at least in later years. Loss of the eyelashes translucent nodules along the lid<sup>300a</sup> and indentation by scars add to the severe disfigurement. Especially in young persons some of the lesions bear crusts but there is no inflammatory border.<sup>300</sup> The corners of the mouth show vertical grooves.

<sup>294</sup>Urbach, F. and Wiethe. Lipoidosis cutis et mucosae. Virchow Arch. f. path. Anat. 222: 222-249, 1929.

<sup>297</sup>Wier, F. and Rein, C. R. Lipoidosis cutis et mucosae (Lipoid Proteinosis of Urbach). Arch. Dermat. & Syph. 57: 201, 1933.

<sup>298</sup>Maltzberger, M. B. Case of Lipoidosis cutis et mucosae (Lipoid Proteinosis Urbach-Wiethe). Laryngoscope 52: 290-293, 1942.

<sup>299</sup>Ransom, M. J. Lipid Proteinosis (Urbach-Wiethe). Arch. Dermat. & Syph. 47: 201-220, 1942.

<sup>300</sup>Campbell, A. Lipoid proteinosis (Urbach-Wiethe). U. S. N. M. Bull. 92: 690-671, 1944.

There are elevated firm elastic brownish yellowish white or flesh-colored tumors on the extensor surfaces of the elbows and on the dorsal and lateral surfaces of the fingers. They are crowded together in warty mulberry like rough plaques.



Fig. 275.—Lipoidosis cutis et mucosae (lipid proteinosis) (Urbach-Wiethe). Yellow nodular lesions beneath the tongue and infiltration of lower lip. (From Wile U. J. and Snow J. B., *Arch. Dermat. & Syph.* 1917.)

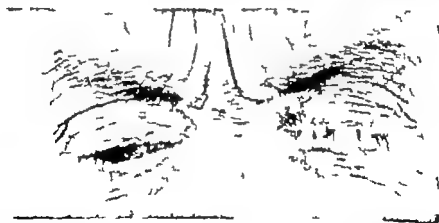


Fig. 276. Lipoidosis cutis et mucosae (lipid proteinosis) (Urbach-Wiethe). Xanthomas pearl with papules along the margins of the eyelids. (From Wile U. J. and Snow J. B., *Arch. Dermat. & Syph.* 1917.)

In some cases the papules undergo early involution, persisting only on the elbow, the knees and the hands. The lips show on their inner surfaces fairly firm, yellowish white plaques. Similar plaques and streaks occur on the palate, in the pharynx, and on the under surface of the tongue, which is rigid and limited

in its motion by a deep seated infiltration and thickening of the frenulum. The papillae are mostly lost.<sup>100</sup> Similar thickening symmetrically involve the tonsils and the larynx.

In the majority of the cases either glycosuria or latent diabetes is present. Heredity seems to play an important role. Consanguinity of the parents and familial occurrences are on record. Congenital hoarseness and developmental defects have also been observed.

Laryngotomy because of severe dyspnea from scarring has become necessary in several cases.

There can be no doubt that this is a characteristic syndrome. The outstanding histological features in both the skin and in the mucosa are (Wise and Rein<sup>101</sup>) an infiltration with a lipid substance surrounding the vascular walls with massive deposits and vacuolization of the infiltrating masses seen in paraffin section. Foam cells and double refraction indicating cholesterol esters are absent. The infiltration consists of a lipid probably bound to a protein.

Bürger and Grün<sup>102</sup> described a severe lipodystrophy with extremely high lipemia, hepato-splenomegaly and a chronic eruption of small yellow, elevated nodules on the extensor aspects and the buttocks. The lesions mainly contained phosphatides but no foam cells and no doubly refractile lipids.<sup>103</sup>

Gaucher's Disease is a slowly progressive often hereditary, chronic lipidosis involving the spleen, the liver and the bone marrow. An uneven brownish-tan pigmentation especially on the parts is usually noticeable. Chloasma like often symmetric patches as well as streaky patterns have been seen.<sup>104, 105</sup> Such symmetrical pigmentations may form quite characteristic leaden-gray reticular gross patterns on the lower legs dotted with more intensely pigmented spots. In advanced cases the skin of the pigmented areas of the legs is glossy and scaly, sometimes ulcerated. These pigmentations leave the soles, heels and toes free but they involve the instep areas in a sharply outlined spat-like fashion.<sup>106</sup> There is a striking free margin just below the ankle. Leg ulcers without varicose veins occur. The mucous membranes may be pigmented but this is supposed to occur only if the adrenals are affected by the lipid deposits. The pigment is melanin. Brownish yellow triangular conjunctival thickenings occupying the interpalpebral space on both sides of the corner but leaving a thin white stripe around the cornea appear slowly in the second decade. These pingueculae together with bone changes and splenomegaly establish the diagnosis.<sup>107</sup> Purpura tendencies occur at times.<sup>108</sup> The specific lipid of Gaucher's disease which fills the large Gaucher cells in the involved organs is kerosin.

Niemann Pick's Disease is another rare familial splenomegalic lipoidosis characterized by enormous accumulations of the dilaaminophosphatide sphingomyelin in the entire reticuloendothelial system. The disease is fatal within the

<sup>100</sup>Erdos, L. Lipoid Proteinosis (Urbach-Wiethe). *Dermatologica* 55: 373-396, 1947.

<sup>101</sup>Bürger, M. and Grün, O. Ueber hepato-splenomegale Lipodystrophie mit xanthoelastischen Veränderungen in Haut und Schleimhaut, *Arch. f. Dermat. u. Syph.* 190: 343-373, 1933.

<sup>102</sup>Gleason, T. F., Gross, J. and Postma, O. Gaucher's Disease, *Quart. J. Med.* 5: 217-237, 1936.

first two years of life. The skin<sup>1909, 1911</sup> of the infants is described as wrinkled, pale and profusely sweating. The subcutaneous fat disappears entirely. The exposed parts and also the mucous membranes are diffusely pigmented, and pigmented patches also occur in the mouth. The pigment is melanin and possibly due to adrenal involvement.<sup>1909, 1911</sup>

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<sup>1909</sup>Pick, L. Niemann-Pick's Disease and Other Forms of So-called Xanthomatosis, *Ann. J. N. Sc.* 188: 601-616, 1933.

## CHAPTER XXX

### METABOLIC DISORDERS

#### Hemochromatosis

*Hemochromatosis*<sup>100</sup> *pigmentary cirrhosis in diabetes* and *bronzed diabetes* are terms mostly used to designate a disease characterized by the production of pigment in almost all organs—diabetes in 78 per cent of the cases and hepatic cirrhosis. The disease occurs almost exclusively (95 per cent<sup>100</sup>) in men, mostly in the decade from 45 to 55 years. The disease was encountered five times among 100,000 hospital admissions.<sup>101</sup> The onset is in accord with the symptoms of diabetes, with abdominal pain or pigmentation of the skin.

The course depends on the diabetes and the cirrhosis. Before the advent of insulin about fifty per cent of the patient died in diabetic coma. Today the prognosis seems better since the outcome mainly depends on the course of the cirrhosis, which may be protracted.<sup>102</sup> Primary cancer of the liver occurs in 7 per cent.<sup>100</sup>

No specific treatment is known and though insulin may lengthen life the disease is ultimately fatal.

The striking pathological feature is the abundant production of pigment which is deposited in almost all organs though in varying amount. The most heavily affected organs are the liver, the pancreas, the adrenal, the salivary gland, and the lymphatic nodes. There are two pigments present: *Hemosiderin* gives the iron reaction and *hemofuscin*<sup>103</sup> is an iron-free melanin. The iron content of the organ, which have been mentioned, at the sites of the main deposit may be a hundred times higher than normal.

The etiology is not known. Familial occurrence has been observed.<sup>104</sup> Sheldon, who has reviewed 345 cases in a comprehensive monograph, classifies hemochromatosis as an *inborn error of metabolism* concerning the cells which later in life begin the cirrhosis of the liver and of the pancreas.

*Neuromas.* The skin participates in the general process of *pigmentation* though not nearly as much as the liver and the pancreas. *Discoloration* is absent in only one sixth of the cases. The *melanoderma* develops insidiously and is the initial complaint in about one fourth of all instances.<sup>105</sup> It may precede the diabetic and hepatic symptoms by many years.<sup>106</sup> It is more

<sup>100</sup> von Recklinghausen, F. *Hemochromatose*. Verh. Deutsch. Naturforsch. 1887. Deutscher Naturforsch. Congr. Heidelberg 1887. Verh. deutsch. Naturforsch. p. 324, 1887.

<sup>101</sup> Reekton, J. B. *Hemochromatosis*. London, 1937. Oxford University Press.

<sup>102</sup> Cal, J. C. *Hemochromatosis*. S. Cases, Texas Stat. J. Med. 26, 226-262, 1910.

<sup>103</sup> Butt, H. R. and Wiedner, W. M. *Hemochromatosis*. A Report of Thirty Cases Diagnosed During Life. Proc. 8. aff. Meet. M. J. Clin. 22, 623-627, 1907.

<sup>104</sup> Lawrence, R. D. *Hemochromatosis and Heredity*. Lancet 2, 1033, 1925.

<sup>105</sup> Becker, A. W. *Shamberg's Disease Associated With Hemochromatosis*. Arch. Derm. & Syph. 24, 340-352, 1921.

often diffuse than patchy or freckled. In many instances the pigmentation covers the entire body but it is more pronounced in the parts exposed to the light and in the axillae, the nipples, the umbilicus and the genital region. As in Addison's disease, scars may become heavily pigmented.

The color varies considerably.<sup>206</sup> In about twenty per cent of the cases the color is described as bronze, ranging from a light bronzing to deep brown and even black. An equal group is characterized by the presence of a gray slate or bluish hue with a metallic reflection. The face tends to acquire a metallic sheen more readily than the body which usually remains brownish. The *metallic component* is more often seen in advanced cases. The oral *mucosa*, particularly of the cheeks, is often pigmented. The discoloration is more spotty than diffuse being brown or slate. The lips and conjunctivae may also become pigmented.

Except for the pigmentation the skin is not much changed. Dryness, scaliness and pruritus may be troublesome.<sup>207</sup> *Parpura* occurs in about fifteen per cent.<sup>207</sup>

Of great interest are the symptoms which indicate *endocrine* influences. They include atrophy of the testes and prostate, impotence, loss of axillary and pubic hair and thinning of the beard, eyebrows and chest hair.<sup>207</sup>

The pigmentation of the nipples and of the genitals must be interpreted in the same way. Deficiency of urinary androgen and of adrenal cortical hormone has also been found. These endocrine features seem to be accompaniments of the hepatic cirrhosis which is such an important part of the syndrome (see hepatic cirrhosis).

The pigmentation increases with the progress of the disease. Improvement has only rarely been reported, most often in connection with insulin treatment.<sup>206</sup>

As is the case in other organs, the skin pigment is composed of hemodermin and hemofuscin. The hemodermin appears microscopically in fine granules most densely accumulated in the membranae propriae of the sweat glands and in the vascular endothelium while the hemofuscin appears in coarse deposits in the epidermis and in the corium. The ratio of the two pigments varies.<sup>208</sup> In some cases the hemofuscin is entirely absent (Roth after Kaufmann<sup>209</sup>).

An *iron reaction in the living skin* has been devised by Fishback.<sup>207</sup> Intra dermal injection of a mixture of equal parts of 0.5 per cent potassium ferrocyanide and one-hundredth normal HCl produces a wheal which turns deep blue in the presence of iron after five minutes.

*Diagnosis* see Table I

### Alcaptonuria and Ochronosis

A rare hereditary metabolic disorder in which the oxidation of the amino-acids tyrosin and phenylalanin is disturbed is called *alcaptonuria*. The urine

<sup>206</sup> Walker, *Pigmentochromia* (Bronsedihabetes) *Edl.* 20: 131.

<sup>207</sup> Merz, R. E. and Ferris, H. W. *Diastochromatosis and Parpura*, *Arch. Int. Med.* 50: 222-229, 1922.

<sup>208</sup> Labbé, M., Boulin, R. and Uhry, P. *Diabète bronze, ou atrophie des organes génitaux et état des pelis (syndrome hépato-puérvo-génital)* *Bull. et mémo. Soc. méd. d. hôp. de Paris* 80: 1574-1577, 1923.

<sup>209</sup> Fishback, H. R. *Clinical Demonstration of Iron in Skin*, *J. Lab. & Clin. Med.* 25: 95-99, 1933.

darkens on exposure to the air because of its content of homogentisic acid. This formation of pigment is closely related to the formation of melanin under normal and pathological condition. After a long duration of alkaptonuria a dark iron free pigment—melanin like in character<sup>123</sup> is deposited in the connective tissues predominantly in the tendons and cartilages. Virchow called this condition *ochronosis*. The *ochronotic* tissues cause characteristic surface dis-



Fig. 277 Ochronosis. Slate-colored spots in ear. At right nose in remifermation. Note dark cartilages. From Phil B. J. W. J. A. M. A.



Fig. 278 Ochronosis. Slate-colored spots indicating the insertion of the tendons of the extraocular muscles.

colorations wherever they are superficially enough situated. This is the case in the sclerotics where slate-colored or even black scleral spots appear on both sides of the cornea but separated from the limbus corneae by a narrow white strip. Thus 4 *triangular figures* with dark centers result. Obviously the site of these spots denotes the underlying insertion of the tendons of the rectus muscles. The influence of light may enhance the pigment formation.

Slit lamp microscopy reveals deposits of pigment in the *cornea*<sup>3973</sup> Other though less frequent and conspicuous gray-greenish or even black discolorations are seen in the *ear* particularly the anthelix and concha, the tip of the nose and in the upper eyelids. Transillumination of the ears makes the cartilages visible as dark shadows.<sup>3979</sup> The ear ducts and the nasal septum may also be discolored. The cerumen may be black<sup>3977</sup> and homogentisic acid has been found in it.

*Diffuse pigmentation* of the face sometimes to the degree of bronzing bluish discoloration of the knuckles, the palmar eminences and the contact surfaces of the fingers have been observed.<sup>1138, 3977, 3978</sup>

The *prognosis* depends on the development of destructive arthritis which occurs in the later stages.

Chronic *phenol poisoning* from prolonged wet dressings with 1 — 3 per cent carbolic acid may produce the same changes as spontaneous ochronosis.

The *morbid anatomy* in fully developed cases is dominated by the black discoloration of the entire cartilage system.

A low protein diet is advised in the management of ochronosis.<sup>38</sup>

### Hyperuricemia—Gout

*Purine substances* are ingested mainly with liver and other viscera fish eggs and other foods rich in nucleoprotein. A certain amount is synthesized in the body. The end product of purine metabolism in the human organism is *uric acid* which is excreted in the urine mostly as urates.

Gout is an unexplained disorder of the purine metabolism. The values of the normal as well as the gouty uric acid level in the blood vary remarkably. Figures over 2.5 mg per cent<sup>3975</sup> over 4.5 — 6 mg per cent<sup>41, 3994, 3995</sup> and over 8.5 — 9.5 mg per cent are samples of what is considered *hyperuricemia* by various authors. Deposits of urates in various tissues especially in and around joints<sup>3992, 3993</sup> are a characteristic feature. Heredity seems to play a part.<sup>3994</sup> Ninety five per cent of the gout patients are *males*. About 5 to 8 per cent of the patients with joint disease have gout.<sup>39, 3996</sup> It is still—as in Sydenham's time—<sup>3996</sup>

<sup>3993</sup>Smith, J. W. Ochronosis of Sclera and Cornea. Oculopigmenting Alkaptonuria. Review of Literature and Report of 4 Cases. J.A.M.A. 126: 1273-1283, 1942.

<sup>3994</sup>Svirsky, M. Y. Ochronosis—Case With Alkaptonuria and Melanuria. Clinica 2: 1232-1233, 1944.

<sup>3995</sup>Feinstein, T. Ueber Ochronose bei Menkesche ad Tiern, Beitr. z. path. Anat. allg. Path. 66: 246, 1910.

<sup>3996</sup>Pick, L. Ochronose. Ber. klin. Wchnschr. pp. 478, 509, 536, 561, 1908.

<sup>3997</sup>Kiesel, J. and Haden, R. L. Gout, Review of 63 Cases. M. Clin. North America 24: 420-441, 1940.

<sup>3998</sup>Talbot, J. H. Gout. New York, 1945 Oxford University Press.

<sup>3999</sup>McCracken, J. H. 30 Cases of Gout. Bull. New England M. Center 3: 249-251, 1941.

<sup>4000</sup>Hench, V. S. Gout in U. S. A. Free Stag Meet., Mayo Clin. 12: 302-309, 1937.

<sup>4001</sup>Hench, V. S. Diagnosis and Treatment of Gout and Gouty Arthritis. J.A.M.A. 119: 432, 1941.

<sup>4002</sup>Bailey, W. and Klempner, F. Medical Progress in Gout. New England J. Med. 221: 631-635, 1944.

<sup>4003</sup>Hench, V. S. The Diagnosis of Gout and Gouty Arthritis. Proc. Stag Meet., Mayo Clin. 11: 476-480, 1936.

<sup>4004</sup>Sydenham, Th. The Works of Thomas Sydenham, vol. 2, London, 1680, Sydenham Society pp. 122-123.



Fig. 279



Fig. 280

Fig. 279.—Goat, dormant opus

Fig. 280.—Goat.

to some extent true that a higher social status (arthritis divicuum of the old physicians) predisposes to gout<sup>2287,2288</sup> Though manual work and poverty do by no means protect against the trouble. Most writers agree that overindulgence in certain foods, as is common in the holiday season may precipitate an acute attack<sup>2420</sup> in a gouty person.

The clinical picture of gout is dominated by repeated acute and extremely painful attacks of arthritis mostly in the small joints. Involvement of one big toe (podagra) is a frequent event. In spite of the acute inflammation there is no suppuration and complete restoration to normal function is the rule. The urinary excretion of urates is subnormal before and in the initial phase but increases rapidly during the attack.

In the chronic stage the attacks occur more frequently and last longer. More and also bigger joints become affected and urate deposits deform and destroy the articular cartilages. Tophi as the demonstrable deposits of urates are called often appear in the neighborhood of joints, in and around tendons in the ears and occasionally in the subcutis.

Kidney function is often disturbed. The prognosis depends on the amount of articular damage renal complications and the degree of cooperation by the patient in avoiding such foods which are prone to cause attacks. Colchicine relieves the acute attack, and cinchophen improves the output of uric acid in the interval although many consider it too toxic. Salicylates are widely used as a less dangerous substitute. Hench<sup>2440</sup> calls the therapy of gout, which has not advanced since the advent of cinchophen a reflection on medical progress.

**Dermadromes**—The ruddy complexion and obesity<sup>2473</sup> of the typical gouty man are often mentioned. Sydenham spoke of his thick shaggy eyebrows and his full crown of hair<sup>2490</sup>. The older literature emphasized and probably overrated the importance of gout in the etiology of dermatoses. Today to a large extent due to the skeptical attitude of J. Jadassohn (1905) who called the evidence scanty and uncertain the only recognized skin manifestation of gout is the tophus of the skin. The tophi are rarely present before or during the first attacks, but they are almost invariably seen in chronic gouty arthritis.<sup>2422</sup> Tophi in connection with the skin are seen in about one third of the cases about the small joints and on the ears. They are often found on the lateral aspects of the fingers, but also about the elbows, knees and heels. On the ears where they occur in the vast majority of the cases of tophaceous gout<sup>2441,2491</sup> they most frequently occupy the helix. The tophi are nontender very firm nodules of varying movability. The size varies from a few millimeters to one centimeter in diameter but they are occasionally much larger. The color of the skin over superficial tophi is pale yellow. The nodules may ulcerate and in the contents microscopic needle-shaped crystals of sodium urate may be found.<sup>1200,2491</sup>

<sup>2287</sup>McCracken, J. F. Owen, Ph. R. and Pratt, J. H. Gout, Still Forgotten Disease. J.A.M.A. 131: 367-372, 1946.

<sup>2288</sup>Brackner-Mortensen, K. 100 Gouty Patients, Acta med Scandinavica 200: 81-107, 1941.

<sup>2420</sup>Radcliffe, D. J. and Redard, R. E. Criteria for the Diagnosis of Presumptive (Pseudogout) Gout, Management of an Hysterical Case. Proc. Staff Meet. Mayo Clin. 131: 148-150, 1937.

<sup>2440</sup>Lichtwitz, L. Gout, Bull. New York Acad. Med. 39: 308-319, 1934.

<sup>2491</sup>Christopher, F. and Mourer, K. E. Tophi of Ears. J.A.M.A. 110: 2149, 1934.

The diagnostic value of typical tophi is great. Many clinicians have stressed looking at the ears in all cases of painful arthritis.

Pruritus is a frequent symptom of gout.<sup>12</sup> W. N. Goldsmith<sup>13</sup> calls gout the most frequent cause of itching which certainly is not true in the U.S.A. Pruriginous eruption, urticaria and papular and bullous lesions have occasionally been seen paralleling the level of the hyperuricemia.<sup>14</sup> Sheaves of urate crystals were found in the lesions in some cases of papules and nodules of the skin of the lower legs.<sup>15</sup> The same is true of psoriasis,<sup>16</sup> erythromelalgia<sup>17</sup> and especially of eczema. Kromayer<sup>18</sup> the last to report a large series of gouty eczema, gave its criteria in obstinacy, recurrence in the same spot, location in unusual places not subject to external irritation, multiplicity of patches and the coexistence of various arthritic and neuritic complaints. Unfortunately his diagnosis and definition of gout are not up to the present standards but one should not dismiss lightly his impressions nor those of other experienced clinicians. Garrod (after Bulkley<sup>19</sup>) found that 47 per cent of 2000 patients with gout had eczema. Bulkley<sup>1</sup> considered fully 30 per cent of his eczema patients as gouty.<sup>21, 22</sup>

Despite these impressive figures the relationship of gout and eczema remains controversial. It is now generally considered of small importance.

The blood uric acid in eczema—and for that matter also in pruritus, psoriasis and urticaria—varies with a tendency to increased levels, especially in severe cases.<sup>23</sup> There is good reason to assume that in some of these cases the inflammatory and destructive processes in the skin are likely to be the cause of the hyperuricemia rather than its sequel.<sup>24</sup> Injections of uric acid into the blood of patients with eczema have been shown not to influence the skin lesions.<sup>25, 26</sup>

Symmetrical hyperkeratosis of the hands and soles together with erythema of the palmar eminences has been seen in several cases of hyperuricemia.<sup>27</sup> This condition occurs alone and also together with several internal disorders, e.g. hepatic disease, the menopause and pregnancy, so that no specific significance can be attached to the dermatosis. Many observations, mostly older than twenty years, are concerned with the role of hyperuricemia in psoriasis. Zorn<sup>28</sup> found that the scales in psoriasis contain a hundred times the amount of uric acid in the blood. He advises a purine free diet in eruptive psoriasis.

Thomas and collaborators<sup>29</sup> have described an alopecia of the anterolateral aspect of the lower legs about corresponding to the area supplied by the

<sup>12</sup>Conzel, F. *Pruritus uraticus. Über Hauterkrankungen bei Gicht* 70 1092, 1929.

<sup>13</sup>Richter, W. *Harnsäure Diathese in Verbindung mit Hautkrankheiten*, Dermat. Wehnacht 101 1867, 1923.

<sup>14</sup>Zorn, H. *Erythroid Psoriasis and Gout*, Dermat. Wehnacht 96 621-623, 1922.

<sup>15</sup>Starkel, J. *Erythromelalgia. Associated With Chronic Gout*, Arch. Dermat. & Syph. 86 72-74, 1924.

<sup>16</sup>Kromayer, K. *Eczema und Harnsäure Diathese*, Deutsche med. Wehnacht 61 1827-1829, 1923.

<sup>17</sup>Stroph, U. and Fölke, O. *Hyperemische Untersuchungen bei Hautkrankheiten*, Med. Monat. 20: 1007-1012, 1924.

<sup>18</sup>Michael, J. C. and Nicholas, H. O. *The Behavior of Injected Uric Acid in Patients With Eczema*, Arch. Dermat. & Syph. 28 309-313, 1926.

<sup>19</sup>Garrod, H. W. *Gout. Vol. I. Treatment*, Proc. Roy. Soc. Med. 28 701, 1925, also 28 497, 1925.

<sup>20</sup>Thomas, L. *Alopecia of Peroneal Regions as Constitutional Sign of Gouty Arthritis*, Disch. Brit. J. Dermat. 22: 1-9, 1910.

peroneal nerves together with slight atrophy of the skin and common baldness. These easily detectable hairless patches are supposedly suggestive of a high blood uric acid level.

### Calcinosis of the Skin

It is difficult to characterize the internal disorder whose skin manifestations represent the various forms of cutaneous calcium deposits.



Fig. 221.—Calcinosis cutis. (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)

An exception is the metastatic calcinosis in which calcium deposits in the skin (striae) and other organs can be related to destructive bone disease e.g. osteomyelitis<sup>121</sup> or myelogenous leukemia (Wels after Sutton and Sutton<sup>122</sup>).

The term *chalk gout* (Winkowski after Steinitz<sup>123</sup>) is based on the similarity of nodular calcium deposits about small joints to the tophi of true gout. It is misleading in so far as an analogy to the uric acid metabolism in gout is not sufficiently apparent in the calcium metabolism in calcinosis.

<sup>121</sup>Jadassohn, J. Ueber Kalkmetastasen in der Haut, Arch. f. Dermat. 100: 217, 1912.

<sup>122</sup>Steinitz, H. Calcinosis circumscripta und Calcinosis universalis, Ergbn. d. inn. Med. u. Kinderch. 22: 516-572, 1931.

*Cutaneous calcinosis* occurs in two quite different types (Verse after Steinitz<sup>117</sup>) with relatively few transitional forms. In the so-called chalk gout or *calcinosis circumscripta* the calcium deposits appear as circumscribed nodules mostly about the terminal phalanges of the fingers and on the extensor aspects of the elbows. The volar surface of the finger tips is often the first location.<sup>118</sup> The legs are rarely affected except for the patellar area. The size of the nodules ranges from mustard seed to pea or even walnut size. Multiple deposits may simulate shots in the X-ray picture. The nodules are usually nontender. Acute painful inflammations of the para-articular tissues resembling gout may occur but they leave the joints and bones free.<sup>119</sup>

Superficial nodules may ulcerate and extrude calcareous material. The mouth of such sinuses is often surrounded by a hard yellow ring.<sup>120</sup> The nodules may become raised globular tumors<sup>121</sup> or the covering skin may be depressed and atrophic.



Fig. 242 Localized calcinosis. Scarria and sinus formation. (Courtesy Dr. G. Cooper.)

On the whole chalk gout in itself is not a severe disorder. The nodules may disappear spontaneously.<sup>118, 119</sup> Life is rarely in danger. However 40 per cent of the cases<sup>122</sup> are combined with scleroderma, Raynaud's disease and acrodermatitis atrophicans.

<sup>117</sup>Epstein, E. Idiopathic Calcinosis Cutis. *Arch. Dermat. & Syph.* 31: 367-377, 1938.

<sup>118</sup>Maloney, E. R. and Bloom, H. Cutaneous Calcinosis. *Arch. Dermat. & Syph.* 23: 245, 1931.

<sup>119</sup>Quincke, W. W. Ferriar, W. G. and Job, V. Calcinosis Circumscripta. *Am. J. Dis. Child.*

43: 390-393, 1923.

<sup>120</sup>Weber, F. P. Improvements in Cases of Calcinosis Universalis in Children. *Brit. J. Dermat.*

47: 400-404, 1933.

<sup>121</sup>Atkinson, F. R. B. and Weber, F. P. Cutaneous and Subcutaneous Calcinosis. *Brit. J. Dermat.*

53: 297-310, 1935.

The female patients with chalk gout outnumber the males about 6 to 1. The disease occurs most often in persons beyond the thirty fifth year of life and the onset has repeatedly been seen connected with the menopause<sup>228-231</sup>. It appears rarely in the young<sup>232-233</sup> at lactation or at puberty<sup>233</sup>. Familial occurrence is known<sup>232</sup>.

In the *diffuse* variety of calcinosis known as *calcinosis universalis* any part of the skin may become affected though there is a tendency to involve the neighborhood of the big joints. Symmetry is a feature and a decrease in the number of deposits towards the acra is often apparent.



Fig. 293.—Male aged 53 years. Large subcutaneous calcareous plaque existing for many years. See secondary infection and sinus formation.

The lesions develop in crops with fever and general reactions. The course is progressive so that finally almost the entire skin may become involved. Large calcareous plaques in or under the skin may form and ulcerate. Deeper structures may become affected and a septic syndrome with fever immobility of muscles multiple chalk abscesses and cachexia may result. The evacuation of large chalk abscesses may improve the picture. In some cases, several quarts of chalky matter could be drained from huge cold abscesses.<sup>234</sup> In chronic

<sup>228</sup>Strandell Birger and Henselman, H. H. Ein Fall von Kalklicht, *Hygiea* 94: 848-851, 1922.  
274 43 467

<sup>229</sup>Pontepidan, B. Subcutane Kalkmassen bei postglomerulärer Nephritis, *Kongressber.* 64: 12-13, 1921. 274 1 419

<sup>230</sup>Gubrower H. Beitrag zur Frage der Kalkabscessen in der Haut, *Dermat. Wchnschr.* 60: 113-6, 1923.

<sup>231</sup>Jacobowitz H. Eine besondere Verlaufsform bei Calcinosis subcutanea, *Kongr. I. Klinisch.* 53: 297-301, 1922.

<sup>232</sup>Gerbards C. Ueber Kalklicht, *Fall. Diss.* 1831 Marburg a. d. L.

<sup>233</sup>Wilmersbach, R. J. Francon, F. and Robert, P. Calcificationes subcutaneae et articulo. *Arch. Pathol.* 1922 11: 29-32.

cases a combination of sinuses scars and ulcerations creates a picture which resembles scrofuloderma. The prognosis is generally unfavorable<sup>214</sup> though long remissions and occasional cures have been observed. Combination with scleroderma has been seen in 32 per cent of the cases of calcinosis universalis.<sup>217</sup> The disease is more frequently encountered in young persons and children<sup>215</sup> than in middle or advanced age.<sup>216</sup>

Rosenberg<sup>214</sup> Brooks<sup>217</sup> and other writers who recently reviewed the subject feel that neither the theory of the deposition of calcium due to a disturbed calcium metabolism in analogy to uric acid in gout nor the theory based on the assumption of the deposition of calcium in already damaged tissues<sup>211,212</sup> have been convincingly proved. The bony skeleton is usually intact and the blood chemistry has been found normal.<sup>219</sup> Experimental hypercalcemia did not in the work of most of the experimenters lead to deposits.<sup>220</sup> Except in scleroderma which accompanies only about 40 per cent of all the cases of calcinosis pre-existing degeneration or necrosis has not been discovered. In these cases the calcium metabolism is often disturbed.

No specific treatment is known. Abscesses should be drained since general improvement has occasionally followed. A diet low in calcium seems sensible. None of the many procedures which have been tried on theoretical grounds<sup>221</sup> has been confirmed or accepted.

Hypocalcinosi has been seen associated with impetigo herpetiformis and pustular psoriasis. (See chapter Parathyroids.)

### Amyloidosis

Amyloid is a protein which may occur in the skin<sup>222</sup> in a primary dermatosis (lichen amyloidosus) in the course of other especially senile dermatoses<sup>223</sup> or in certain tumors. Much rarer is cutaneous amyloidosis as part of the generalized amyloidosis which develops in chronic cachexias especially tuberculous. Cutaneous nodules<sup>224</sup> and erythematopigmentary or erythromelalgic changes<sup>225</sup> have occasionally been recorded but they seem to be very rare. Also very rare

<sup>214</sup> Rémy Roux. Sur un cas de granulomies calcarees sous-cutanees. Bull. et méém. Soc. de radiol. méd. de France 29: 437-440, 1932. Ebi 43: 834.

<sup>215</sup> Hangerstrand, H. Calcinosis universalis bei einem Kinde. Ebi 84: 203, 1936-1937.

Rosenberg E. F. Calcinosis. J. A. M. A. 118: 1791-1794, 1940.

<sup>217</sup> Brooks W. D. W. Calcinosis. Quart. J. Med. 3: 293-319, 1934.

<sup>218</sup> Thannhauser, J. Lehrbuch des Stoffwechsels und der Stoffwechselkrankheiten, München, 1929. J. F. Bergmann, p. 603.

<sup>219</sup> Bleiweiß Hagemann, E. Die Calcinosen der Haut unter Berücksichtigung einer Fülle von Aecrocalcinose. Dtsch. H. n. b. 1933, H. n. b. 1933.

<sup>220</sup> Friedländer, J. L. Versuche über den Gesamtmineralschmelze bei Calcinosis universalis. Dtsch. Arch. f. klin. Med. 194: 107-121, 1930.

<sup>221</sup> Oesterreich, od. Carreton. Contribution à la pathologie des granulomies calcarees. Absence de réactions inflammatoires. Absorption des sels calcarees injectés loin des lésions et dans les lésions. Bull. Soc. franc. de dermat. et syph. 29: 704-706, 1932.

<sup>222</sup> Zankhander, G. La dépression amyloïde de la cut. Ober. Ital. di dermat. 74: 1499-1524, 1933.

<sup>223</sup> Prendental, W. Amyloid in der Haut. Arch. f. Dermat. u. Syph. 193: 40-84, 1930.

<sup>224</sup> Alibekson, H. E. and Lynch, F. W. Systematized Amyloidosis of the Skin and Mucous. Arch. Dermat. & Syph. 29: 803-830, 1934.

<sup>225</sup> Fleming, N. F. and, J. and Albaharry, C. U. cas d'amylose hépatique et cutanée. Bull. et méém. Soc. méd. d. hôp. de Paris 96: 274-278, 1943.

is a peculiar form of *systemic amyloidosis* which not only produces an unusual dermatosis, but follows a different pattern in the distribution of the amyloid avoiding the spleen and the large glands which in the typical cases contain the largest deposits of amyloid. Instead the smooth and the striated muscles



Fig. 224.



Fig. 225.

Fig. 224—Localized amyloidosis. (Courtesy Division of Dermatology Department of Medicine University of Chicago.)

Fig. 225—Amyloidosis cutis (liver amyloidosis). (Courtesy Dr. H. E. Kitzredge.)

Including the heart are the site of widespread amyloidosis<sup>222-223-224</sup>. Enlargement, fissuring and nodularity of the *tongue* was present in all cases. There may be difficulty in closing the mouth and the *gait* may be shuffling. The clinical aspect of the skin in some of the cases<sup>222-223-224</sup> is characterized by *transparent* or yellow waxy small high firm papules which cover some areas very densely

<sup>222</sup>Leberich, O. Zur Kenntnis ungewöhnlicher Amyloidablagerungen, Virchows Arch. f. path. Ana. 271: 367-389, 1929.

<sup>223</sup>Kolaczek, H. Amyloid der Haut, Handb. d. H. u. Gh. 4 3: 234-257, 1932.

<sup>224</sup>O'Leary, F. A. Montgomery, H. and Brunsting, L. A. Systemic and Amyloidosis of the Skin, and Mucous Membranes. Deane-Jones Proteinuria, Arch. Dermat. & Syph. 31: 406-409, 1934.

<sup>225</sup>Bowdler, S. L. Sobre l'amiloidosis cutanea, Cook's Dermat. pp. 67-82, 1931. Ed. 44: 476.

<sup>226</sup>McGow, W. Zur Klinik der systematischen Amyloidose, Verhandl. d. deutsch. Gesellsch. f. inn. Med. pp. 333-336, 1930.



The eyelid, scalp, the pubic and adjoining areas, the palms, the dorsa of the feet and other sites have been seen covered with the lesions which at first glance because of their transparency give the impression of vesicles. Atrophy, telangiectases and purpuric spots are other features. In some cases the lesions were very firm large nodules<sup>711, 712</sup> or large sclerodermatic plaques.<sup>714</sup>

All the patients were middle-aged or older.<sup>712</sup> Multiple myeloma and Bence Jones proteinuria have been found in some cases.<sup>712</sup>

The presence of amyloid in the living skin can be demonstrated by the subcutaneous injection of 0.1 per cent solution of congo red in saline. The produced red spot fades within 4 days in normal skin but remains visible up to 12 days if amyloid is present at the site of injection.<sup>712, 713</sup>

The amyloid forms a band in the upper cutis, the epidermis being atrophic and free of amyloid. The vascular walls and the muscles contain large deposits. The apken and the large glands have no amyloid or only along the blood vessels.

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Gottlieb, H. *Arterio sklerose und Hämorrhagien der Haut im Alter*. Die Haut mit charakteristischen Veränderungen. II. Berlin, 1912. Urban & Schwarzenberg, pp. 23-37.

Reich, H. *Erkrankungen unter dem Erscheinungsbild einer Sarkoidose abgrenzte Amyloidose der Haut*. Zbl. 7, 1927, 191.

Reich, H. *Amyloidose der Haut*. Zbl. 80, 1928, 1977.

Reich, H. *Wie man die Haut Metastasenamyloidose von einer Amyloidose des Kollagenes unterscheidet*. Arch. f. Derm. & Syph. 100, 1-2, 1932.

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## CHAPTER XXXI

### METABOLIC DISORDERS

#### Vitamin Deficiencies

**A Itaminoals A**—Vitamin A is a fat-soluble heat-resistant unsaturated alcohol which is easily destroyed by oxidation. It is formed in the liver from its precursors the yellow or red carotenes which occur in widely differing amounts in fruits, vegetables and animal fats. The daily vitamin A requirement of the human organism is 3000-5000 I. U.

Deficiency of vitamin A causes night blindness because the visual purple and the visual violet develop from Vitamin A. Xerosis conjunctivae is another early ocular symptom occurring together with the cutaneous epithelial changes. A specific protective function of vitamin A against infections, which was assumed earlier<sup>127-129, 134</sup> is now doubted.<sup>135-137</sup>

The most often used test for vitamin A deficiency is the measuring of the dark adaptation of the eyes. This is done by determining the threshold amount of light which must be used to illuminate a given surface in order to render it visible. The readings after light and dark adaptation are then compared.<sup>138-140</sup> The value of the dark adaptation test for vitamin A deficiency has recently been questioned.<sup>141</sup> The determination of the concentration of vitamin A in the blood plasma will probably be a better indicator of deficiency than the dark adaptation,<sup>139</sup> but so far only little work with spectrophotometric determinations of the vitamin A content in connection with skin changes has been done.<sup>142</sup>

The fat droplets containing vitamin A are highly fluorescent in ultraviolet light, but lose this property rapidly in ultraviolet light.<sup>143</sup> Surprisingly enough

<sup>127</sup>Wichard, F. Ueber die Bedeutung der Vitamine in der Dermatologie. *Skt. 44* 657-681, 1933-1934.

<sup>128</sup>Ebert, M. H. Vitamins in Dermatology. *M. Clin. North America* 26: 47-61, 1942.

<sup>129</sup>Platzekstiel, W. and Scharian, B. Der Einfluss gesteigerter Vitaminzufuhr auf experimentelle Atrophieekthymatome der Haut. *Zeitschr. f. d. ges. exper. Med.* 71: 463-476, 1930; *Skt.* 35: 622.

<sup>130</sup>Platzekstiel, W. Weitere Versuche über den Einfluss von Vitaminen und Calcium auf experimentelle Atrophieekthymatome der Haut. *Zeitschr. f. d. ges. exper. Med.* 77: 213-223, 1931; *Skt.* 38: 200.

<sup>131</sup>Stensberg, Th. and Wilbury H. M. Influence of Avitaminosis A on Experimentally Produced Cutaneous Infections in Rats. *Arch. Dermat. & Syph.* 58: 247-250, 1937.

<sup>132</sup>Bramming, L. A. and Sheard, C. Dark Adaptation in Psoriasis. *Brit. J. Derm.*, *Arch. Dermat. & Syph.* 43: 42-61, 1941.

<sup>133</sup>Carlson, A. and Steven, D. Keratotic Folliculitis. *Arch. Dermat. & Syph.* 48: 182-189, 1943.

<sup>134</sup>Wakere, J. D. Dark Adaptation in Skin Conditions. *Ohio Stat. M. J.* 44: 324-336, 1944.

<sup>135</sup>Reck, H. M. Henshaw, L. A. and Osterberg, A. E. Use of Vitamin A Tolerance Test in Certain Cases of Dermatoecic Disorders. *Proc. Staff Meet. May Clinic* 21: 209-217, 1944.

<sup>136</sup>von Quersner, F. Der mikroskopische Nachweis von Vitamin A im animalen Gewebe. *Klin. Wchnschr.* 14: 1513-1517, 1935.

In examinations with the fluorescence microscope vitamin A has been found to be absent from the epidermis even after the feeding of high doses<sup>111</sup>

It is likely that vitamin A is concerned with the lipid. Experimental hypervitaminosis A results in accumulation of cholesterol in the adrenals, the skin and other organs<sup>112</sup> so that lesions develop which are comparable to those of Schüller-Christian's disease. Circumscribed alopecia is also a feature of this experimental disease.



Fig 296. Infant 18 months of age. Follicular hyperkeratotic cells in vitamin A deficiency (hypertrophial cells). From Frazier (N. H. C. K. and Chu, P. T.; *Arch. Dermat. & Syph.* 1943.)

**Dermadromes**—Hyperkeratinization as an effect of vitamin A deficiency on the epithelium has been known for a long time (Mori after Schan<sup>113</sup>). In the rat it leads to the appearance of keratinized cells in the vaginal mucosa, a phenomenon resembling estrus.

In the human skin the effect of vitamin A deficiency are also dominated by hyperkeratinization<sup>114</sup>. Dryness caused by impaired function of the keratinized oil and sweat glands is the first symptom (Frazier and Hu<sup>115</sup> and Inde-

<sup>111</sup>Corableet, Th. and Pepper, H. Properties of Human Skin Revealed by Fluorescence Microscopy. The Normal Skin. The Vitamin A Content of the Skin, *Arch. Dermat. & Syph.* 44: 59-65, 1943.

<sup>112</sup>Cañero, J. A. and Rodriguez, J. Hypervitaminosis A durch Fütterung von reinem A Vitamin an junge Ratten, *Klin. Wchnschr.* 12: 1732-1734, 1933.

<sup>113</sup>Maschkileton, L. B. Beryanovich, E. B. Krichovskaya, E. B. and Shumova, L. V. Vitamin in Pathogenesis and Treatment of Skin Diseases, *Am. Rev. Soviet Med.* 3: 18-27, 1943.

<sup>114</sup>Frazier, O. N. and Hu, O. K. Cutaneous Lesions Associated With Deficiency in Vitamin A in Man, *Arch. Int. Med.* 60: 507-514, 1931.

pendently Loewenthal<sup>120</sup> described a characteristic dermatosis which occurred frequently in persons who had lived on a diet deficient in vitamin A and who suffered from night blindness, keratomalacia and/or xerophthalmia. The eruption which was called *phrynoderma* or toad skin by Nicholls<sup>121</sup> healed after treatment with vitamin A or an adequate diet.



Fig. 267 — Male aged 14 years. Diffuse follicular hypertrophies (*phrynoderma*) in vitamin A deficiency (From Frazer C M H O A. and Chas. F T Arch. Dermat & Syph., 1943)

Phrynoderma consists of disseminated somewhat grouped *perifollicular* papules with a central keratotic plug or spine. In severe cases<sup>122</sup> the papules are large flat or hemispherical sometimes acneiform without suppuration sometimes more like lichen planus. Slate colored hyperpigmentation may occur in and around the lesions. The eruption is usually abundant and symmetrical predominantly appearing first on the anterolateral aspect of the thighs and the

<sup>120</sup>Loewenthal, L. J. A. A New Cutaneous Manifestation in the Syndrome of Vitamin A Deficiency Arch. Dermat & Syph 28 700-709, 1933

<sup>121</sup>Nicholls, L. Phrynoderma. A Condition Due to Vitamin Deficiency Indian M. Gaz 68 641-666, 1933

<sup>122</sup>Paul, F. Clinical Manifestations of Vitamin Deficiency: the Malay States, Arch. Dermat & Syph 66 180-186, 1944

posterolateral aspect of the upper part of the forearms spreading from here to the extensor surfaces of the arms and legs, the shoulders, abdomen, chest, back and buttocks.<sup>214</sup> Itching is a frequent complaint. There is absence of visible sweating so that the articular folds become dry and scaly. Diffuse branny scaling "ashing" is also often noticeable especially in Negroes.<sup>214</sup> The colored skin is apt to lose its natural sheen.<sup>215</sup> The lack of oiliness helps to differentiate this papular eruption from acne.

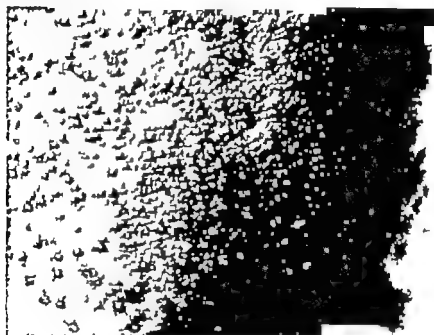


FIG. 204. Male aged 16 years. Follicular hyperkeratosis, follicular hyperkeratosis of vitamin A deficiency. From Frazee C. N., H. C. K. and Chu P. T. Arch. Dermat. & Syph. 1952.

Comedones are common not only in adolescents but also in older persons. Brittleness and grooving of the nail<sup>216, 217</sup> is a feature of avitaminosis A. Loss of luster of the hair caused by dryness and alopecia are frequently observed phenomena.<sup>214, 218</sup>

Phrynoderma usually precedes the *ophthalmic symptoms*<sup>219</sup> which sometimes are completely absent. Pillat<sup>220</sup> describes a characteristic pigmentation of the

<sup>214</sup>Lehman E. and Rapaport, H. O. Cutaneous Manifestations of Vitamin A Deficiency in Children. J. A. M. A. 114: 396-397, 1940.

<sup>215</sup>Reiss, F. Contribution. Cutaneous Manifestations of Vitamin A Deficiency. *Chirurgia M. J.* 89: 845-847, 1936. *Klin. W.* 88: 878.

<sup>216</sup>O'Call, Alopecia Circumscripta Due Vitamin A Deficiency Case. Arch. Dermat. & Syph. 81: 110-111, 1945.

<sup>217</sup>Pillat, A. Ernährungstheorie. Edited by W. Stepp. Berlin, 1939. Julius Springer.

<sup>218</sup>Frazee C. N. and H. C. K. Nature and Distribution According to Age of Cutaneous Manifestations of Vitamin A Deficiency (307 Cases). Arch. Dermat. & Syph. 23: 825-832, 1934.

<sup>219</sup>Pillat, A. Ueber eine eigenartige Pigmentierung der Hautoberfläche bei den verschiedenen Formen der Vitamin A-Mangelkrankung der Erwachsenen. Graefes Arch. 227: 878-897, 1931.

conjunctivae most marked in the caruncula plica semilunaris, and the lower fornix. The pigmentation may outlast the deficiency state after treatment with vitamin A.



FIG. 296.—Follicular hyperkeratosis in vitamin A deficiency with xerophthalmia. (From Frazer C. M. Ha. C. K. and Chiu, F. T. Arch. Dermat. & Syph. 1943.)

The histopathologic features are epithelial hyperplasia and hyperkeratinization with associated follicular keratinization and degeneration of the hairs as well as of the sweat and oil glands<sup>236,237</sup>. There is some inflammation in the corium but no pustulation. The disease is not rare among children<sup>238</sup> as had been originally assumed. The closer the age groups are to puberty the more likely they are to be affected.<sup>239</sup> This is in line with the well known tendency to follicular keratosis in acne juvenilis.

Among children with xerosis of the skin without phrynodermia the testes are equally affected. In adult groups the patients are almost exclusively males.<sup>240</sup> Straumfjord<sup>240</sup> has tried to explain the formation of vernix caseosa by the absence of the antikeratinizing vitamin A in later fetal life. A small group of pregnant

<sup>236</sup>Jones, F. H. Histopathology of the skin in Avitaminosis A. Arch. Dermat. & Syph. 47: 784-777, 1943.

<sup>237</sup>Frazer, C. M. Ha. and Chiu. Variations in Cutaneous Manifestations of Vitamin A Deficiency From Infancy to Puberty. Arch. Dermat. & Syph. 98: 1, 1943.

<sup>238</sup>Straumfjord, J. A. Vernix Caseosa: A Manifestation of Vitamin A Deficiency. West. J. Surg. 48: 1-3, 1940.

women who were treated with high daily doses of vitamin A during the last six months of pregnancy had babies with less vernix than usual.

The response of phrynoderma and the other dermatoses to dietary treatment and vitamin A in daily doses of 100 000 to 300 000 I. U. is usually prompt within two to four months. The sebaceous secretion was often restored within two weeks. The recognition of a follicular keratosis as a specific manifestation of vitamin A deficiency by Frazier and Wu stimulated investigation of the nature of other follicular keratoses. Peck<sup>213</sup> found in eight out of ten cases of Darier's disease the blood vitamin A below normal and in nine cases he was able to improve the hyperkeratotic symptom of this hereditary disease which up to then had been largely considered incurable. The vitamin A level in the blood rose under treatment with approximately 200 000 units daily.

Peck<sup>213,214</sup> believes Darier's disease to be a congenital disorder of the absorption of the vitamin A or of the conversion of carotene by the liver into the final product. Peck's work has been confirmed in several instances,<sup>215,216</sup> of this rare dermatosis but resistant cases have also been found.<sup>217</sup>

The follicular keratosis in *psoriasis rubra pilaris* (Devergie's disease) prompted Brunsting<sup>218</sup> and Sheard to analogous investigations. In three cases the threshold level of dark adaptation were much higher than normal. Under vitamin A treatment the night blindness and later also the cutaneous changes improved materially. The vitamin A content of the blood has several times been found low.<sup>219,216</sup> The good results of treatment with vitamin A have been confirmed in some cases.<sup>21</sup> 270

Treatment with vitamin A has been found beneficial in various forms of excessive or abnormal keratinization particularly in dermatoses which have the features of dryness (asteatosis) and follicular or other hyperkeratosis such as acne vulgaris, calluses, corns,<sup>222,223</sup> pruritus kraurosis vulvae,<sup>224</sup> lichen pilaris,<sup>214</sup> keratotic lichenoid plaques of the legs, ichthyosiform erythroderma in Hodgkin's Disease with hepatic involvement,<sup>225</sup> scaldiness of the external auditory canal,<sup>226</sup> nummular eczema,<sup>22</sup> brittleness of the nails,<sup>210</sup> dryness of the skin in diabetes<sup>227</sup> and keratosis blennorrhagica.<sup>22</sup> It has been recommended in ointments for the treatment of burn and low healing wounds and ulcers.<sup>212</sup> The

<sup>213</sup>Peck M. Chang L. and Seiboth H. Keratosis Follicularis (Darier Disease) Vitamin A Deficiency Disease Arch. Dermat. & Syph. 43: 222-229 1941

<sup>214</sup>Peck H. Keratosis Follicularis (Darier Disease) Treated With Vitamin A Arch. Dermat. & Syph. 45: 632-638 1945

<sup>215</sup>Corabian T. Popper H. and Clemens F. Blood Vitamin A and Cutaneous Disease. Arch. Dermat. & Syph. 48: 103-106 1944

<sup>216</sup>Weiner A. L. and Levin A. A. Psoriasis Erythrodermia of Familial Type Arch. Dermat. & Syph. 43: 294-298 1943

<sup>217</sup>Stranford J. V. Vitamin A Effect on Acne Northwest Med. 42: 219-223, 1943

<sup>218</sup>Obermayer M. E. and Frost K. Some Phases of Vitamin Therapy in Dermatology Arch. Dermat. & Syph. 51: 308-312 1945

<sup>219</sup>Glassbrook A. J. and Tomaszewski W. Ichthyosiform Arophy of the Skin (Hodgkin Disease) Vitamin A Metabolism Arch. Dermat. & Syph. 50: 45-49 1944

<sup>220</sup>Jones J. H. Vitamin Therapy Laryngoscope 53: 801 1943

<sup>221</sup>Gross P. Nummular Eczema, Arch. Dermat. & Syph. 46: 1000-1077 1941

<sup>222</sup>Deaver J. H. and Curtis A. C. Vitamin A Deficiency in Diabetes Arch. Int. Med. 85: 80-106, 1940.

<sup>223</sup>Lohr K. Die Behandlung grosser flächenhafter Verbrennungen mit Lebertran. Chirurg 6: 262-270 1924.

cod liver oil containing salves are an example. Vitamin A in high doses has been found ineffective in ichthyosis.<sup>113</sup>

All the mentioned indications cannot yet be considered established.<sup>114</sup> The therapeutic doses of vitamin A range from 50 000 to 200 000 units daily. In spite of the fact that the blood serum level of vitamin A has been frequently



Fig. 200.—*Pityriasis rubra pilaris*. (Courtesy Dr. M. Jansen.)

found to be low in widespread dermatitis, eczema and proriasis, no curative effect of vitamin A therapy could be observed in such cases.<sup>115</sup> The level of vitamin A in the blood plasma of 55 patients with diverse dermatoses was essentially normal.<sup>116</sup>

<sup>113</sup>Peck, L. V., Glick, A. W. and Chargin, L. Vitamin A Studies in Cases of Ichthyosis, *Arch. Dermat. & Syph.* 48: 7-22, 1943.

<sup>114</sup>Marchionini, A. and Patel, G. Vitamin A—und Curingehalt des menschlichen Bluteserums bei Hautkrankheiten, *Arch. f. Dermat. Syph.* 175: 19-27, 1937.

<sup>115</sup>Corabiet, Th., Pappier, H. and Steinmann, P. Blood Vitamin A and Cutaneous Diseases, *Arch. Dermat. & Syph.* 49: 102-108, 1944.



**Carotenemia Xanthoid** —*Carotinemia aurantiasis* (Baeltz after Kaufmann<sup>117</sup>) or *xanthosis* (Von Noorden and Salomon) after Salomon<sup>117</sup> (manifests itself by a yellow discoloration of the serum and of large area of the skin. The yellow color which may have canary, ochre or sulfur shades suggests at first glance icterus but the sclerae are white and the mucous membranes are usually of normal color with the exception of the palate. Another distinguishing feature is the distribution of the yellow pigmentation. The nasolabial fold, the axillae and the palms and soles are the sites of the most intense discoloration, in slight cases the only sites. In contrast to icterus pruritus is absent unless caused by diabetes. There are no complaints other than the disfigurement.

The urine is light compared with an icteric urine although carotene is excreted in the urine.

The history and physical examination almost regularly reveal that the patient had lived for a long time on a vegetarian diet that he is a diabetic or both.

The yellow substance which causes the discoloration has long been identified as carotene. The carotenes are red orange or yellow oxygen free hydrocarbons with 40 C-atom which by hydrolysis form the alcohol vitamin A. All green leaves (not the yellow leaves in fall) carrot pumpkin yellow squash oranges especially some Japanese varieties and many other fruits contain carotenes. Animals are unable to form carotene but they take it in and store it in the liver, the fat, the retina, the corpus luteum and the adrenal. It causes the yellow color of the butterfat, the body fat and of the egg yolk. Carotene does not appear in the sweat.<sup>118</sup> The horny layer of the epidermis has a marked affinity for carotene which explains the normal yellow hue of the palms, soles and calluses.<sup>119</sup>

Carotinemia has often been seen in babies fed with carrot. It was frequently observed during the First World War in Germany<sup>117</sup> where at times most of the population was compelled to live almost exclusively on rutabaga, carrots and other vegetables. It is also prevalent in the Japanese inland where the fish and meat supply is scanty. After feeding infants with carrots for a very long time the carotinemia may disappear in spite of continuing with the diet. The system apparently adjusts itself and becomes able to step up the splitting of carotene. The alimentary carotinemia particularly in infants is harmless and disappears quickly after a change in the diet (Diabetic carotinemia see chapter on Diabetes).

**Vitamin D** (cholesterol and activated 7-dehydrocholesterol) is stored mainly in the liver but also in the skin and in other organs. One of the known functions of vitamin D is the maintenance of the absorption of calcium and phosphorus from the intestinal tract.<sup>120</sup> The most important vitamin D deficiency disease is rickets.

No dermatosis caused by vitamin D deficiency has been established. Therapeutic success with daily doses of 50 000 to 400 000 unit has been reported in

<sup>117</sup>Salomon, H.: *Pseudokritik nach Melantherogenese*, München und Weinsack 99, 354, 1, 19.

<sup>118</sup>Kaufmann and Orskov: *Carotin-Vitamin A im menschlichen Organismus*, Kln, Weinsack

12, 304-308, 1923.

<sup>119</sup>Edwards E. A. and Denney R. Q.: *Pigments and Color of Living Human Skin*, Am. J. Anat. 95, 1-33, 1929.

perniphigus<sup>212,213</sup> but confirmation has remained lacking<sup>212</sup> The treatment has also been given a trial in psoriasis<sup>212,213</sup> and acne vulgaris. Though 80 per cent satisfactory results were claimed in a large series<sup>214</sup> the method has not found general recognition<sup>215</sup>

Vitamin E comprises a group of more than 130 substances.<sup>177</sup> Experimental avitaminosis E manifests itself by sterility muscular dystrophy paralysis and other symptoms according to the animal used. Many seed germ oils, particularly that of wheat, contain vitamin E, which has so far not become of recognized dermatological importance. Its successful use in acrodynia has been reported<sup>216</sup>

Vitamin K (menadione) occurs most abundantly in green leaves, e.g. spinach alfalfa and cabbage. It is also synthesized by several bacteria e.g. *Escherichia coli*. Its absence inhibits the prothrombin formation in the liver. When the prothrombin drops to about 10 per cent of normal in chicks kept on a vitamin K free diet the bleeding tendency appears<sup>217</sup>. In man obstructive jaundice through the absence of bile salts in the intestines impairs the absorption of adequate amounts of vitamin K and thus creates hypotherbunemia with a subsequent hemorrhagic tendency (Brown and Bancroft 1935 after Quick<sup>218</sup>). Therefore the picture of avitaminosis K is that of hemorrhagic disease which may cause purpuric skin manifestations. In the adult it results most often from severe disease of the liver from short-circuiting operations or chronic diseases of the intestinal tract. For the role of vitamin K in the hemorrhagic disease of the newborn see chapter on newborn page 394

**The Vitamin B Complex**—According to Elvehjem<sup>219</sup> the B complex consists of at least a dozen separate factors which vary widely in their chemical structure and physiological effects. Deficiency in any one of the B-vitamins is usually complicated by a deficiency in another B-vitamin or by a deficiency in some other vitamin<sup>220,221</sup>

<sup>212</sup>Buttsworth T. Perniphigus. Improvement Following Vitamin E. Arch. Dermat. & Syph. 41: 620, 1941

<sup>213</sup>Kling, H. and Hamilton, C. M. Perniphigus Controlled by Vitamin E. Arch. Dermat. & Syph. 40: 18-217 1939

<sup>214</sup>Wright C. R. Vitamin E Therapy in Dermatology. Arch. Dermat. & Syph. 43: 143-184 1940.

<sup>215</sup>Lindsay H. C. Psoriasis Arthropathica Treated With Vitamin D. Arch. Dermat. & Syph. 41: 621 1940

<sup>216</sup>Maynard. Vitamin Therapy I. Dermatology Especially Vitamin D for Acne. Arch. Dermat. & Syph. 41: 2-587 1940

<sup>217</sup>Stamper, C. Ellis, F. A. and Kirby Smith, H. Vitamin D in the Treatment of Acne. Arch. Dermat. & Syph. 41: 635-637 1940

<sup>218</sup>Forrest G. Chick Disease Treated With Wheat Germ. M. J. Australia 1: 77, 1942. Abst. Arch. Dermat. & Syph. 46: 173

<sup>219</sup>Quick A. J. The Coagulation Defect in Sweet Clover Disease and in the Hemorrhagic Chick Disease of Dietary Origin. A Case History of the Source of Prothrombin. Am. J. Physiol. 118: 260-271 1937

<sup>220</sup>Elvehjem, O. A. Water Soluble Vitamins. Handbook of Nutrition Chicago 1943 American Medical Association

<sup>221</sup>Wolfe M. Recent Advances in Clinical Application of the B-Vitamins. J. Am. Dietet. A. 17: 2-11 1943

<sup>222</sup>Wolfe, T. D. Brown, W. B. and Ashe W. F. A Note on the Use of Vitamin B<sub>12</sub> in Human Nutrition. J. A. M. A. 122: 2414-2418, 1939

A vitamin B deficiency should be suspected in indigent groups in persons with peculiar food habits e.g. alcohol addicts, in persons who live mainly on sweets and in dietary faddists and in patients with diseases altering the vitamin B requirement. Jolliffe<sup>211</sup> mentions in this connection prolonged abnormal strain, manic depressive psychoses, fever of long duration, hyperthyroidism, pregnancy, lactation, rapid growth, diarrhea of long duration, polyuria, gastrointestinal fistulae and liver and stomach diseases.

**Thiamine**—The richest sources of thiamine are yeast, pork, oatmeal, peanuts and other seed and liver. Spinach, tomatoes, oranges, apples and white unfortified bread are poor in this vitamin. Without the use of whole grain cereals or enriched bread it is difficult to meet the adult daily requirement of 1.3 to 2.3 mg.<sup>212</sup> Symptoms of thiamine deficiency<sup>213</sup> include anorexia, fatigue, insomnia, nausea, constipation, headache, precordial distress and a group of more tangible neurological manifestations like symmetric polyneuritis especially of the legs followed by central symptom known as Wernicke's syndrome. Finally there occurs a group of circulatory disturbances including edema, serous effusions and circulatory collapse. These circulatory manifestations occur in about one-third of the patient with polyneuropathy. All the mentioned symptom together with their many variations form the *beriberi* complex.



Fig. 291. (Soles and perleche in riboflavin deficiency. Courtesy Dr. O. H. Field, J. and The Upjohn Company.)

The only well established early and therefore important skin manifestation in *beriberi* is the burning of the soles of the feet and numbness of the dorsum and lower part of the ankle.<sup>214, 215</sup> Glucitis perleche<sup>216</sup> and other skin manifestations probably belong to associated avitaminoses. The expected pain relieving

<sup>211</sup>Jolliffe, L. B. Burning Feet in Labourers on Sugar Plantations in British Guyana. *J. Trop. Med.* 53: 354-360, 1939.

<sup>212</sup>Stearns, H. B. Article in *The Vitamins*, Chicago, 1939. American Medical Association.

<sup>213</sup>Kagawa, S. Ueber Rhagadenbildung am Mundwinkel bei der B-A-Hemmung, *Mits. d. med. Gesellsch. zu Tokio* 46: 1153-1164, 1912. *Idid.* 43: 630.



Fig. 29.1 — Loss of papillae filiformes and increased redness of the tongue in vitamin B deficiency (Courtesy Therapeutic Notes, Parke, Davis & Company)



Fig. 29.2 Vitamin B deficiency — Loss of papillae filiformes resulting in slick, beaded tongue (Courtesy Wisconsin General Hospital)

and curative effect of thiamin in herpes zoster and postherpetic neuralgia has failed to materialize.<sup>210</sup>

**Riboflavin**—This vitamin is a yellow crystalline heat stable but light labile<sup>211</sup> substance. It functions as an enzyme in tissue respiration. Liver, milk and vegetables are the best sources. The daily minimal requirement can be met with one serving of liver or one quart of milk. Experimental ariboflavinosis causes retarded growth, dermatitis and cataract in rats, paralysis from myelin degeneration in chicks and dogs, and opacities in the cornea of various animals.

**Dermadromes**—In man vascularizing keratitis is usually the first to appear. It may be followed by glossitis and dermatomes. Sebrell and Butler<sup>212</sup> gave eighteen adult women the so-called Goldberger-Tanner diet<sup>213</sup> which does not contain meat, milk or yeast but consists mainly of lard, cornmeal, casein,



FIG. 291. Vitamin B deficiency. First an inflamed, swollen, fissured, and papillary cheilosis has started. Cheilosis has disappeared. (Courtesy Dr. Gary Cooper.)

tomato juice, cod liver oil and other items low in riboflavin and nicotinic acid. Within three to four months ten out of the eighteen persons developed pallor of the lips at the angles of the mouth without involvement of the buccal mucosa. This pallor was soon followed by maceration. Unilateral superficial transverse fissures extending downward from the angle in some instances as much as one half of an inch. Thus typical perleche developed. There was little inflammatory reaction. The lesion remained moist and became covered with a yellow crust. The lips became eroded and red along the line of closure. Sebrell and Butler<sup>212</sup> called this labial affection *cheilosis*. In addition to the cheilosis there was a fine seborrheic desquamation on a light erythema in the nasolabial folds on the alae nasi, in the vestibule of the nose and on the ears.

<sup>210</sup>Richter H. and Hall H. Herpes Zoster and Vitamin B. J. A. M. A. 112: 2535-2540, 1939.

<sup>211</sup>Sebrell, W. H. and Butler R. E. Riboflavin Deficiency in Man, Pub. Health Rep. 53: 2252-2254, 1938.

<sup>212</sup>Goldberger J. and Tanner W. F. Pellagra—Prevention: Action of Dried Beans, Corn, Dried Milk and Brewer's Yeast. Pub. Health Rep. 68: 51-60, 1923.

Other authors<sup>2180,2187</sup> observed *filiform excrescences of a seborrheic nature* in the nasolabial folds and their surroundings resembling urea frost in conditions which they felt to be due to riboflavin deficiency.

The experimental cheilosis healed promptly on crystalline synthetic riboflavin while nicotinic acid failed to cure it. Spontaneous cases of cheilosis are not infrequently found among alcoholics and other persons liable to become vitamin B deficient. Jolliffe<sup>2187</sup> et al demonstrated that many of these spontaneous cases of cheilosis responded to synthetic riboflavin but not to thiamin, nicotinic acid or pyridoxin (also see Finnerud<sup>2182</sup>).

In some cases of ariboflavinosis the tongue has been found purplish red fissured and with enlarged papillae.<sup>2189</sup> Riboflavin in doses of 2.5 to 50 mg given by mouth heals cheilosis from riboflavin deficiency sometimes strikingly in a few days<sup>128</sup> but of course fails to do so when the perlèche or cheilitis are due to other causes<sup>2188</sup> e.g. ill fitting dentures or sensitivity to light. Cheilosis is also a common feature of pellagra in children.<sup>2190</sup>

Sydenstricker<sup>2191</sup> and others have described *ocular symptoms* especially an early vascularizing keratitis accompanied by inflammation of the limbic plexus and conjunctiva bulbi in the interpalpebral space. Photophobia is a characteristic complaint. The slit lamp is necessary for early diagnosis. The keratitis resembles the form often associated with rosacea but it is bilateral, responds to riboflavin and shows a different vascular pattern.

The validity of the syndrome cheilosis, keratitis and glossitis as a manifestation of ariboflavinosis has recently been doubted because of the failure of riboflavin to cure it in 20 cases.<sup>2192</sup> Riboflavin has lately been recommended in the treatment of eczema.<sup>2193,2194</sup>

Rats with chronic hyporiboflavinosis showed in contrast to other avitaminoses a heavy infestation with lice which disappeared after feeding them riboflavin.<sup>2195</sup>

**Nicotinic Acid (Niacin). Pellagra.**—Nicotinic acid (niacin) and nicotinic acid amide (niacin amide) are the components of two pairs of heat stable (Chick and Roscoe<sup>2196</sup>) coenzymes concerned with respiration and carbohydrate metabolism.<sup>2197</sup> A deficiency disease in dogs called blacktongue has, since the work of Goldberger and his coworkers in the early twenties, been con-

<sup>2180</sup>These pseudo-seborrheic changes should not be confused with seborrheic dermatitis, which is accompanied by oily hair and skin.

<sup>2187</sup>Jolliffe N., Feix, H. D. and Rosenblatt, L. A. Riboflavin Deficiency in Man, New England J. Med. 231: 921-928, 1939.

<sup>2188</sup>Finnerud C. W. Perlèche: Its Nosologic Status, J.A.M.A. 128: 737-740, 1944.

<sup>2189</sup>Jolliffe N. The Preventive and Therapeutic Use of Vitamins, J.A.M.A. 129: 612-617, 1945.

<sup>2190</sup>Chen, M. C. Riboflavin Deficiency Among Chinese: Cheilosis and Seborrheic Dermatitis, Chinese M. J. 79: 814, 1941; Abstr. Arch. Dermat. & Syph. 68: 381.

<sup>2191</sup>Sydenstricker E. P., Sebrell, W. H., Cheekley H. M. and Kruse, H. D. Ocular Manifestations of Ariboflavinosis, J.A.M.A. 116: 2437-2448, 1940.

<sup>2192</sup>Marbella, Th. K. and M. Donald, H. R. B-Vitamins in the Human Subject. VI. Failure of Riboflavin Therapy in Patients With the Accepted Picture of Riboflavin-Deficiency. Am. J. M. Sc. 260: 814-823, 1943.

<sup>2193</sup>Landier J. Y. Deficiency of Vitamin B. Lancet 1: 1269-1270, 1939.

<sup>2194</sup>Kristensen, K. P. and Vondet B. V. Treatment of Eczema With Vitamin B Complex, Lancet 1: 179, 1940.

<sup>2195</sup>Gyorgy P. Pediculosis in Rats Kept on Riboflavin-deficient Diet. Proc. Soc. Exper. Biol. & Med. 36: 812, 1933.

<sup>2196</sup>Chick, H. and Roscoe M. H. Heat-Stability of Vitamin B. Biochem. J. 24: 104-112, 1930.

sidered analogous to human pellagra. In 1937 Elvehjem discovered that nicotinic acid would cure canine blacktongue. Deficiency of nicotinic acid is generally believed to be the main cause of pellagra though clinical pellagra is considered now to be a multiple vitamin deficiency<sup>227, 228</sup> which is often associated with symptoms of beriberi<sup>229</sup> ariboflavinosis<sup>230</sup> (Hou after Ottenstein)<sup>231</sup> sprue<sup>232</sup> and scurvy.

Liver and yeast are the richest natural sources of nicotinic acid. Corn contains only about one fifth of the niacin content of wheat and the refined flours of both grains lose almost the entire amount. Nevertheless even refined wheat flour still contains three times as much niacin as refined corn flour. The peculiar scarcity of niacin in corn accounts for the frequency of pellagra in countries where the diet of the poor consists predominantly of corn flour products. The first medical writer on pellagra, the Spaniard Casal in 1762, already suspected the use of corn flour in the poor peasant population as one of the causes of pellagra<sup>233</sup>. We know now that other deficient diets may cause pellagra too. Alcoholism and chronic gastro-intestinal disease are the most important causes of pellagra in countries without endemic pellagra<sup>234</sup>. Among 102 cases in Baltimore about one-third were due to alcoholism, one-third due to malnutrition and one-third secondary to other diseases.<sup>235, 236</sup> Chronic gastric ulcer, cancer of the stomach and surgical removal of large parts of the stomach or bowel are conditions which predispose to pellagra<sup>237</sup>.

The main centers of endemic pellagra are found in some warm mediterranean countries and in the southern U.S.A. The tropics as well as the cooler climates have only sporadic cases mostly alcoholics, insane or patients with gastric disorders. The incidence has become smaller in the main centers e.g. Italy<sup>238</sup> (Lavinder after Seale Harris<sup>239</sup>) where the morbidity of 104,067 in 1881 had diminished to 55,029 in 1905 probably due to improved living and eating conditions. At the same time the mortality was reduced to about one tenth. Thus in the last decades pellagra has become a rare disease in the classical pellagra country. A decided trend to the better also prevails in the southeastern U.S.A. where the incidence has been reduced by more than 50 per cent from 1929 to 1936<sup>240</sup>. Today pellagra is no longer a major public health problem.

- <sup>227</sup>Gordon, E. R. and Arrington, E. L. *Vitamin Therapy in General Practice* Chicago 1940.  
The Year Book Publishers Inc.  
<sup>228</sup>Elvehjem H. A. Role of Nicotinic Acid. *Pellagra, Physiol. Rev.* 20: 219 1940.  
<sup>229</sup>Albers F. H. *Pellagra*, Nederl. Idsch. geneesk. pp. 910-950 1923. Ed. 48 187.  
<sup>230</sup>Mydenricker, V. P., Owsdin, L. E., Tenpleton, O. M. and Wren, J. W. Riboflavin Deficiency in Human Subjects. *J. A. M. A.* 118: 1097 1935.  
<sup>231</sup>Harris. *Clinical Pellagra*, St. Louis 1911. The C. V. Mosby Co.  
<sup>232</sup>Merek, L. *Pellagra*. Ed. 17: 211-265. no. 380-411 1933.  
<sup>233</sup>Klander, J. V. and Winkelmann, W. W. *Pellagra Among Chronic Alcoholic Addicts*, *J. A. M. A.* 90: 364-371 1924.  
<sup>234</sup>Boers, T. R. and Padgett, P. *Pellagra*, 103 Cases. *Bull. Johns Hopkins Hosp.* 50: 21-22, 1922.  
<sup>235</sup>Wheeler, O. A. and Sebrell, W. H. *Control of Pellagra*, *J. A. M. A.* 89: 85-89, 1923.  
<sup>236</sup>Spies, T. D. and de Wolf, H. P. *Observations on the Etiological Relationship of Severe Alcoholism*, *Pellagra Am. J. M. Sc.* 100: 521-525 1923.  
<sup>237</sup>Kosterma, H. D. and O'Leary, P. A. *Pellagra Secondary to Benign and Carcinomatous Lesions and Dysfunction of the Gastrointestinal Tract. Thirteen Cases*, *Arch. Int. Med.* 47: 623-649 1921.  
<sup>238</sup>Latrario, A. *La pellagra qui disparaît en Italie*. *Bull. Office internat. d'hyg. pub.* 25: 83-126, 1926.

in the Union though it is far from being stamped out. In 1938 3 205 deaths from pellagra occurred mostly in the southeastern states. It is remarkable that the southwest has a very low pellagra rate.

The ages between 20 and 45 years seem to be most susceptible (Lavinder after J. Jadassohn<sup>229</sup>) but no age group is immune. Many large statistics show a dominance of the female sex. Menstruation pregnancy and lactation are provoking factors. The distribution of the lesions suggests strongly that sunlight is an important pathogenetic element yet a great number of observations of typical lesions in covered skin (vulva) and of lesions restricted to the typical areas in children who did not wear any clothes prove that exposure to light is not the only provoking factor<sup>230</sup> though one of great importance in the eruptive stage<sup>231</sup> or after a prolonged deficient diet.<sup>232</sup> Some authors even claim a beneficial influence of sunlight in pellagra in some stages<sup>233</sup> (for extensive discussion of the sunlight factor see also Seale Harris<sup>234</sup>).

Lack of a gastric, intrinsic anti pellagral factor<sup>235</sup> and failure of the liver to store and utilize nicotinic acid are much discussed pathogenetic factors.<sup>236</sup>

The word *pellagra* is derived from the Italian *pelle agra* sharp burning skin or from the Latin *pellis agra*—sick, unhealthy skin. The skin manifestations however though characteristic do not represent the most serious part of the syndrome.

Usually the disease<sup>237</sup> starts in the spring of the year with increasing latitude and muscular weakness especially of the legs which make the patients slow moving and resort to the use of canes a suggestive symptom well known to physicians in pellagra regions.

Already in this early stage burning of the seemingly still normal skin particularly of the feet, a burning sensation in the throat which cannot be soothed by cold water and other *paresthesias* cause discomfort. The patients avoid the heat and lie uncovered in bed. Headache and sudden attacks of dizziness or falling without convulsions, or nystagmus are typical nervous symptoms. The reflexes are increased the pupils are small.<sup>238</sup> Psychoses of widely varying seriousness develop frequently. The facial expression of the patient is often a worried fearful melancholic or stuporous one.<sup>239</sup> Such patients cry easily and are depressed sometimes in realization of the deterioration of their faculties. In severe cases hallucinations depression even mania, delirium suicidal at

<sup>229</sup>Merck, H. and Jadassohn, J. Die Pellagra. Handb. d. H. Gk. 4, 2 377-447 1923.

<sup>230</sup>Flaker, R. Die Lokalisation der pellagrischen Hautveränderungen. Schwed. med. Wchnscr. 58 150-152 1924.

<sup>231</sup>Smith, D. T. and Rabin, J. M. Effect of Sunlight on the Clinical Manifestations of Pellagra. Arch. Int. Med. 58 631-644, 1937.

<sup>232</sup>Wigles, T. D. Psoriasis Dermatitis and Sunlight. Arch. In Med. 86: 920-926, 1923.

<sup>233</sup>Sydenstricker, V. P. Armstrong, K. S., Derrick, O. J. and Kemp, P. B. On the Existence of an Intrinsic Defect in Pellagra. Am. J. 31, No. 193: 1-6 1936.

<sup>234</sup>Kobayama, H. Beiträge zur Frage der Pellagra. Trich. d. 23 1829-1884 1930. Zbl. 23 732.

<sup>235</sup>Rife, J. H. Die Hanterscheidungen der Pellagra. Dermat. Wchnscr. 58 806-312, 1930 also Zbl. 54 122-130.



tempts and other manifestations of psychoses develop.<sup>223, 224</sup> On the other hand psychosis with a long confinement to institutions is a predisposing factor to pellagra.<sup>225</sup>

The internal symptoms are dominated by various phases of inflammation of the *gastrointestinal tract*. These disturbances most often account for a fatal outcome.<sup>22</sup> The oral symptoms will be described later.

Anorexia is an early symptom. Nausea, vomiting and diarrhea are common though greatly varying in intensity. Free HCl is absent in more than 66 per cent<sup>226, 227</sup> and the pepsin content is low. The stools, no matter of what consistency, are nearly always foul.<sup>228</sup> Anemia is present in about 50 per cent.<sup>229, 230</sup> Diabetes insipidus has been observed frequently. Urinary porphyrin has been found according to the extent and acuity of the skin manifestations. It is a coproporphyrin which has but a weak light sensitizing effect. Porphyrin excretion was



Fig. 245. Pellagra. Extensive dermatitis on right hand following accidental industrial exposure to sunlight. From Harris, Reale. (Clinical Pellagra, The C. V. Mosby Co.)

<sup>223</sup>Metopalsky D. Zum Vorkommen pellagroider Erkrankungen bei Alkoholikern und Geisteskranken. *Schweizer med. Wochenschr.* 63: 297-301, 1933.

<sup>224</sup>Chesler F. Klinischer Beitrag zu dem Problem der Pellagrapsychose. *Zeitschr. f. d. ges. Neurol. Psychiat.* 125: 179-219, 1932.

<sup>225</sup>Georgi F. and Beyer A. Zur Klinik und Genese der Pellagra. *Monatsschr. f. Psychiatrie Neurol.* 76: 295-351, 1930.

<sup>226</sup>Frankel H. Ueber Pellagra in Irrenanstalten. *Psychia.-neurol. Wochenschr.* 28: 461-465, 1932.

<sup>227</sup>Laferla M. and Mayer C. Beitrag zum Studium des Magensaftes bei der Pellagra. Der Einfluss des Histamins auf die Achlorhydrie der Pellagra. *Rev. suisse med.* 19: 2272-2277, 1930. *Zbl.* 28: 237.

<sup>228</sup>Guthrie J. B. Achlorhydria in Pellagra. *J. Trop. Med.* 36: 71-74, 1932.

<sup>229</sup>Flinker R. Das Hirnbild bei Pellagra. *Folia haemat.* 49: 146-154, 1932. *Zbl.* 63: 439.

<sup>230</sup>Turner H. Pellagra. *Arch. Dermat. & Syph.* 26: 690-693, 1932.

<sup>231</sup>Rosenfeld J. A. Diabetes insipidus bei Pellagra. *Arch. f. Schiffs- u. Tropen-Heilg.* 36: 4: 1-100.

found negative in the interval between the attacks.<sup>222</sup> Urinary porphyrin has occasionally been found in alcoholics with or without pellagra.<sup>224</sup> Fever is generally absent but in some cases a spiking fever with diarrhea may create a typhoid-resembling rapidly fatal disease.<sup>227-228</sup>

**Dermadromes.**—Skin manifestations of pellagra appear in the majority of the cases.<sup>221</sup> They do not cause such dangerous complications as the gastrointestinal and neurological symptoms but they are of great diagnostic, even path



FIG. 294.—Earl pellagrous dermatitis over the patellae (Courtesy Dr. Henry Field J., and the Upjohn Company)

ognomonic importance. Together with the sometimes dubious internal complaints they give the syndrome of pellagra its character as a well defined entity.

<sup>222</sup>Beckh, W., Ellinger, P. and Spies, T. D. Porphyrinuria in Pellagra, *Quart. J. Med.* 8: 308-319, 1937.

<sup>223</sup>Kark, R. and Melbye-John, A. P. Pellagra and Porphyrinuria, *Am. J. M. Sc.* 261: 380-388, 1941.

<sup>224</sup>Ginsberg, D. Sporadic Cases of Pellagra in Northern Russia, *Russ. vart. dermat.* 9: 473-488, 1921. *Ibid.* 41: 64.

<sup>225</sup>Margaret, J. and Rimband, P. Typhus pellagrosus. *Bull. Soc. Franc. de dermat. et syph.* 28: 1361-1364, 1921.

The outbreak of typical *pellagra erythema* occurs suddenly, sometimes preceded by a premonitory deciduous macular eruption<sup>221</sup> on the dorsa of the hand. The true erythema of pellagra appears most frequently at first on the dorsa of the hands. In contrast to eczema, this lesion is solid and well defined. Even in sunlight exposed and tanned forearms the pellagra erythema rarely extends higher up than the wrist line. The palms remain free. The pellagra erythema frequently stops at the knuckles, but it may invade the extensor surfaces of the fingers.<sup>221</sup>



Fig. 297 - Pellagra, collar of Casal. (Courtesy Dr. M. J. Jensen.)

Occasionally the erythema affects the flexor aspects in a strap or cuff like bridge. If this occurs it is considered an important diagnostic sign.<sup>222</sup> The instep is the site of an additional erythema. Here the inflammation extends from a line right above the ankles to the base of the toes. In analogy to the hands the dorsa of the toes are only occasionally involved. The erythema may also appear on the face. The bridge of the nose is most frequently erythematous, but diffuse or confluent always symmetric patches may occupy the whole face. In the confluent type polycyclic patterns may appear. Facial erythema is more often encountered in women and children than in men and it is often inconspicuous.<sup>223</sup> Narrow bands of skin along the hair line and around



FIG 908 — Pellagra. Collar of Casal. Chertilla. (From Harris, Seale. *Ocular Pellagra*.)

the mouth remain normal. This mask-like distribution is similar to that of chloasma.

The fourth typical site of pellagral erythema is a ring of varying width around the entire neck. This is called the necklace or collar of Casal. In the typical instances, Casal's necklace extends into the sternal area as a berloque shaped appendix.

The elbows, knees (Bass after Seale Harris<sup>200</sup>), shoulders, scrotum, perineum, vulva and infra-mammary areas<sup>201-210</sup> are some of the less common sites. Sym-

<sup>200</sup>Oosterloo, M. J. Pellagra in Unusual Locations. *Arch. Dermat. & Syph.* 46: 734, 1943.

<sup>201</sup>Kierdan, T. J., Geble, S., and Rubinstein, A. M. Unusual Sites of Lesions in Pellagra. *Arch. Dermat. & Syph.* 46: 641-654, 1943.

metry is a pronounced sometimes astonishing feature<sup>222</sup>. The skin on which the erythema develops is often slightly edematous. At first the erythema consists of confluent pink blotches but within a week it takes on a bright scarlet red color which later has a copper or mahogany hue<sup>223</sup>.

A few days after the appearance of the erythema the epidermis cracks and fissures develop. In some cases vesicles, blisters, pustules and other forms of secondary infection may appear with a predilection for the hair follicles of the dorsa of the fingers. These follicles are often blackened with non-removable

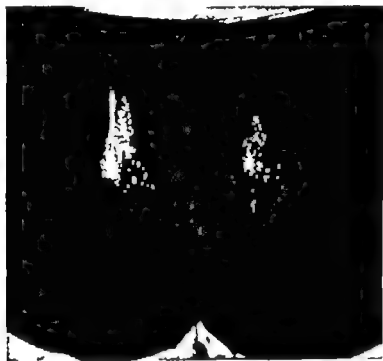


FIG. 299. Vulvitis pellagra. (From Harris, Acute Clinical Pellagra.)

dist. In the early part of the second week the erythema reaches its peak. A pink halo up to 2 cm in width may surround the lesions. A few days later the acute symptoms recede and ichthyosiform keratosis, peeling, deep fissuring and increasing pigmentation become the dominating features. The pattern of ridges and furrows is coarsened. Follicular keratosis appears in the erythematous areas. On the hands they may be inconspicuous but on the bridge, the tip and the sides of the nose and in the nasolabial folds they may form grater-like patterns.

This follicular hyperkeratosis about the nose has been referred to as seborrhea<sup>224</sup>. The facial follicular hyperkeratosis is a frequent and characteristic clinical feature of pellagra<sup>225</sup>.

The centers of the pellagral areas begin to clear up during the fourth week. The horny layer comes off in large flakes, sometimes in sheets of the size of the entire lesion. A scaly hyperkeratotic margin may remain for some time.

The typical attack of pellagra erythema is over in 6 to 10 weeks. Pellagra usually occurs in *repeated attacks* mostly in spring and early summer although recurrences in fall occur occasionally. In winter time the patient is usually free of symptoms. The repeated attacks of erythema on the dorsa of the hands leave the skin in an increasingly *atrophic* condition which of course is not reversible.



Fig. 300. Neglected pellagra. Thickened, fissured and plaquetted lesions extending far beyond the normally involved dorsa of the hand. (From Harris, *Seale Clinical Pellagra*.)

*Longitudinal yellowish stripes* (sometimes referred to as *striae*) are caused by underlying extensor tendon which can be seen through the thin atrophic skin in moderately strong day light<sup>221 222</sup>. *Oral manifestations* occur in about one half of the cases (Sandwith after J. Jadasohn<sup>221</sup>). They are important because some of them e.g. burning and salivation are among the earliest symptoms. The description of the tongue in pellagra vary. Swelling and coating are early



Fig. 201 So-called *ecthyma* of the nose in pellagra. (From Harris, Seale: *Clinical Pellagra*.)

symptoms. Denudation may occur on the margins and on the tip while the dorsum remains coated<sup>221 222</sup>.

In fully developed cases the fungiform papillae may be reddened and swollen (raspberry tongue) or in later stages atrophic, thus giving the appearance of a slick bald thin tongue. Fissures and ulcerations, black hairy tongue, brown coating, ulceration and other lesions have been observed. In acute stages the entire oral mucosa may be fiery red. Aphthous lesions are common<sup>221</sup>.

The *lips* may show small red erosions and there may be angular fissures. Plaut-Vincent's infection of the gums is a common finding in pellagral stomatitis.<sup>204</sup>

*Vaginitis and vulvitis* with much discharge and occasionally edema of the clitoris and labia minora is often called an important or even pathognomonic symptom.



Fig. 302.—Pellagra. Typical dermatitis of the feet and of the patellar regions. (From Harris, *Seale Clinical Pellagra*.)

The *nails* are usually not affected. The *hair* is often shed during the attacks and complete alopecia has been seen to develop. The loss of the lateral part of the eyebrows is frequent and may have some endocrinological significance (see

<sup>204</sup> Kaminsky J. and Barova L. Zur Klinik der Pellagra in Mitteleuropa. Arch. f. Schiffs- u. Tropen-Hyg. 34: 323-336, 1932.





The post mortem *pathology* is unrevealing. The most striking feature is the severe hepatic atrophy or fatty degeneration. As can be expected the skin shows keratosis parakeratosis, pigmentation and atrophy according to the stage. There is degeneration of the elastic fibers and perivascular infiltration and hyalin degeneration of the vascular walls.<sup>234</sup> The unaffected skin also shows hyperkeratosis atrophy and inflammation though in a lesser degree.<sup>235</sup>

The *diagnosis* is a clinical one since satisfactory laboratory methods have not yet been worked out. One has to consider eczema in which there are no mucosal symptoms and no atrophy and erythema exudativum multiforme in which the primary lesion is a coin-shaped erythematous urtica often with a central vesicle. Acrodermatitis atrophicans takes a slow nonseasonal course and has its typical localization and pityriasis rubra pilaris is nonseasonal and there is no pronounced involvement of the typical pellagra sites although niacin is reportedly effective.<sup>237</sup> The diagnosis of pellagra is easy in endemic and fully



FIG. 301.—Atrophic lesion in pellagra. From H. Pitt, Seale: Clinical Pellagra.

developed cases but difficult in sporadic and incomplete cases. The typical sites the sharply outlined lesions the seasonal attacks, atrophy nutritional peculiarities including chronic gastrointestinal disease and alcoholism and the combination of internal and skin manifestations will often assure the diagnosis if its possibility once enters the physician's mind. Incomplete syndromes<sup>234</sup> may cause great difficulties in the differentiation from pernicious anemia<sup>239 240</sup> sprue Addison disease and other entities.

<sup>234</sup>Arztblatt. Is erkrankung zur Erkennung der Pellagra, Dtsch. Woch. 1922, Bd. 48, 457.

<sup>235</sup>Mason H. V., Wpale T. D. and Cooper E. A. Histopathology of the Skin in Pellagra, Arch. Dermat. & yph. 44, 100-111, 194.

<sup>236</sup>Gross, P. Pityriasis Rubra Pilaris and Vitamin Therapy Arch. Dermat. & yph. 44, 270-277, 1940.

<sup>237</sup>Wheeler H. A. A Note on the History of Pellagra in the United States, Pub. Health Rep. 44, 2222-2229, 1943.

<sup>238</sup>Wpale T. D., Payne W. and Chinn A. B. Relationship of Pellagra, Pernicious Anemia, Proc. Soc. Exper. Biol. & Med. 32: 224-230, 1934.

<sup>239</sup>Arztblatt. A. Pitt und Bluthildung bei sehr selten Fällen von Pellagra, Path. Anz. 48, 198-206, (1911) Bd. 48: 82.

As a diagnostic sign one has to add successful treatment with nicotinic acid<sup>234</sup> and a balanced diet. More than one thousand successfully treated cases (nicotinic acid) were reported in 1941 when Seale Harris published his monograph on pellagra. Oral treatment with nicotinic acid in divided doses totaling 300 mg daily supplemented by vitamin B complex and vitamins A, C, D and E, is recommended (Spies, *et al.* after Gordon and Sevringhaus,<sup>237</sup>). After a week 100 mg per day is sufficient. Ruffin and Smith<sup>235</sup> advise injections of about 100 mg daily. Injections and larger doses by mouth are followed by flushing of the face together with a feeling of heat and tingling.<sup>233</sup> This harmless side-effect can be avoided if the nicotinic acid is given with the meals or replaced by nicotinic acid amide.<sup>237</sup>

A high caloric diet with the emphasis on meat, liver, eggs, milk and fresh vegetables, removal from slum housing and reduced exposure to sunlight are other important therapeutic factors. Stomach preparations (ventriculin) have been recommended by several authors.<sup>233, 236</sup> This medication is based on the discovery of an intrinsic pellagra preventing factor in the gastric juice.<sup>233</sup>

The prognosis is now better and recovery is often dramatic unless irreversible damage to the nervous and gastrointestinal systems or severe cachexia has developed. In spite of liver diet or medication the mortality in large American series was still 20 to 31<sup>237</sup> and even 50 per cent<sup>238</sup> 10 years ago but almost zero in private practice.<sup>231</sup> With the use of nicotinic acid and other vitamins the mortality has probably been lowered. Many authors stress the importance of prolonged treatment after clinical cure.

The pellagra preventing effect of nicotinic acid has been proved.<sup>234</sup>

Pyridoxine has been used with encouraging results in the treatment of adolescent acne. The doses varied from 30 to 250 mg daily in divided doses.<sup>239</sup> Seborrhea and an acrodynia resembling syndrome have been seen in pyridoxine deficient rats.<sup>234-236</sup>

<sup>234</sup>H. H. J. 55 and Seale H. D. T. Treatment of Pellagra With Special Reference to the Use of Nicotinic Acid. *South M J* 33: 40-47, 1939.

<sup>235</sup>Gordon, L. C. A. and Sevringhaus. The Vasodilating Effects of Nicotinic Acid. *Am. J. M. Sc.* 208: 304-309, 1943.

<sup>236</sup>Lackard, F. Pellagraproblems. *Med. Clin.* 33: 189-191, 1937.

<sup>237</sup>Petri, S. and Wamacher, O. Treatment of Pellagra and Polyneuritis With Stomach Preparations. *Hospitalstidn.* 79: 1002-1004, 1938. *Id.* 80: 308.

<sup>238</sup>Petri, S. and Wamacher. *Id.* *Id.* Tegshjær, K. and *Id.* Tegshjær, H. P. Treatment of Pellagra With Stomach Preparations and the Gastrogenic Etiology of Pellagra, etc. *Acta med. Scandinav.* 33: 440-481, 1937. *Id.* 39: 316.

<sup>239</sup>*Id.* Tegshjær, H. P. Neurological Problems in Pellagra. Treatment With Ventriculin. *Hospitalstidn.* 80: 441-455, 1937.

<sup>240</sup>Smith, J. H. Pellagra. *Review Internat. Clin.* 3: 120-124, 1933.

<sup>241</sup>deWitt, V. P. and Armstrong, M. B. 440 Cases of Pellagra. *Arch. Int. Med.* 59: 522-531, 1927.

<sup>242</sup>Spies, T. D., Orsak, J. S., Stone, B. E. and M. Lester, J. B. Recent Observations on 800 Pellagras. Nicotinic Acid in Prophylaxis. *South M J* 33: 1231-1237, 1939.

<sup>243</sup>Jodt, N., Rosenblum, L. A. and Seale, H. D. J. The Effects of Pyridoxine (Vitamin B<sub>6</sub>) on Pubescent Adolescents. *Acne J. J. Derm.* 3: 143-148, 1943.

<sup>244</sup>Eichardt, R. E., O'Leary, P. and Johnson, L. V. Presence of Factor in Bile Which Enhances Bacterial Growth Activity in Relation to Riboflavin. *Proc. Soc. Exper. Biol. & Med.* 46: 405-409, 1941.

<sup>245</sup>Phillips, M. and Nichols, J. Nutritional Approach to Experimental Dermatology. *Nutritional Dermatology in the Rat. II. Vitamin B<sub>6</sub> Deficiency.* *J. J. Derm.* 3: 308-343, 1940.

According to Gordon and Sevringhaus<sup>1297</sup> pyridoxine is able to heal cheilosis quicker than riboflavin<sup>1298</sup> Some pellagra cases may heal only after addition of pyridoxine to the other vitamins.<sup>1299</sup> The healing effect in seborrheic eczema atopic dermatitis and eczema<sup>1300</sup> still lacks confirmation

No cutaneous manifestations in man have definitely been related to deficiencies of *panthothemic acid*, *choline* and *biotin*. Panthothenic acid prevents the greying of the hair in rats fed on a B complex free diet<sup>1301</sup> A substance in uncooked eggwhite called *avidin*<sup>1302</sup> is able to inactivate the vitamin *biotin* (vitamin H). Dermatitis of the feet in the chick, and alopecia in rats fed on a diet containing much raw egg white have been observed and some data pointing to analogous phenomena in man are available.<sup>1303,1304</sup> The so-called egg white injury in the rat has been cured by the addition of excess biotin<sup>1305</sup> to the eggwhite-rich diet or by inactivating the avidin by cooking. A *para-amino benzoic acid* deficient diet causes graying of the fur of rats, which can be cured by feeding this substance<sup>1306</sup> There is some evidence that repigmentation of gray hair in man may be stimulated by oral administration of *para-amino benzoic acid* or calcium panthothenate. The changes produced in some persons were only of theoretical value since in the majority of the cases with any change at all an unsightly yellow or greenish cast was produced sometimes together with scattered wavy black hairs.<sup>1307-1312</sup> No satisfactory restoration of the hair color which could compete with dyeing has been accomplished<sup>1313</sup> Some results of prolonged oral medication with *para-amino benzoic acid* in vitiligo have been reported.<sup>1314</sup>

*Inositol* is required to maintain the fur of the mouse.<sup>1315</sup> Stryker and Halbeson<sup>1316</sup> observed that 32 out of 42 cases of unexplained and noncharacteristic dermatitis about the neck and face were accompanied by moderate macrocytic anemia. These cases responded at once to proper diet and liver extract, which in the opinion of the authors was due to the vitamin B complex.

**Avitaminosis C—Scurvy—***Iskatin C* or *ascorbic acid* occurs in many animal and plant tissues especially in the adrenal cortex from which it was first

<sup>1297</sup>MacArthur, Th. R. Studies of the B Vitamin in the Human Subject, *Am. J. Cl. Sc.* 223: 114, 1942.

<sup>1298</sup>Wright, C. S., Hamrick, M. H., and Brown, H. Pyridoxin in Dermatology *Arch. Dermat. & Syph.* 47: 651-663, 1943.

<sup>1299</sup>Umana, K., Richard, O. V. and Sampson, W. L. Studies on Nutri. Achromotrichia (Baldness) in Rats, *J. Nutrition* 22: 543-553, 1941.

<sup>1300</sup>Ostry, P., Rose, C. S., Kahle, R. E., Scott, E. B. and Williams, R. J. Egg White Injury Non-Absorption of Biotin, *Science* 53: 477-478, 1941.

<sup>1301</sup>Sydneystricker, V. P., Stangel, S. A., Briggs, A. F., De Vries, M. M. and Isbell, H. Egg White Injury in Man and Its Cure With Biotin, *J. A. M. A.* 228: 1189-1200, 1942.

<sup>1302</sup>Williams, M. H. Clinical Biotin Deficiency, *New England J. Med.* 224: 247-249, 1943.

<sup>1303</sup>Amacher, F. *p*-aminobenzoic Acid, *Vitamin, Science* 53: 104-105, 1941.

<sup>1304</sup>Brandtke, M., Malm, K. and Steele, J. M. Effect of Calcium Panthoate and *Para*-aminobenzoic Acid on the Gra. Hair of Humans, *Proc. Soc. Exper. Biol. & Med.* 53: 47-49, 1943.

<sup>1305</sup>Wore, B. Clinical Effects of New B-Complex Factor *Para*-aminobenzoic Acid, on Pigmentation and Fertility South Afric. & Surg. 104: 125-130, 1942.

<sup>1306</sup>Can Hair Turn White Over Night? *J. A. M. A.* 221: 16: 102, 1943.

<sup>1307</sup>Eller, J. J. and Diaz, L. A. Vitamins for Gra. Hair, *New York Stat. J. Med.* 43: 1231, 1943.

<sup>1308</sup>Woodbury, D. W. Nature of Anti-Alopecia Factor, *Science* 52: 284-293, 1940.

<sup>1309</sup>Stryker, O. V. and Halbeson, W. A. Determination of Macrocytic Anemia as Aid in Diagnosis of Certain Deficiency Dermatoses, *Arch. Dermat. & Syph.* 51: 110-123, 1943.

isolated. The human body is unable to synthesize ascorbic acid in the necessary amounts and therefore has to rely on the plant sources especially the citrus fruits peppers green leafy vegetables tomatoes and other plant products.

Vitamin C is easily inactivated by oxidation. Cooking storing without refrigeration alkalization and the presence of copper even in traces rapidly diminish the content of active vitamin C. In the organism it is concerned with the maintenance of connective tissue. In scorbutic animals the formation of fibers from fibroblasts is seriously disturbed and the friability of the capillary walls which in clinical scurvy lead to many manifestations of hemorrhagic disease may be explained by the lack of adequate intercellular substances.<sup>1291</sup>

Scurvy: at the present time a rare disease. In adults it is seen following malnutrition among inmates of ill-managed prisons or other institutions in times of famine or after prolonged gastrointestinal disease with restricted diet. Scurvy is more frequent in infants fed on cow's milk especially if the milk is being sterilized by boiling.

In adults general weakness pain in the legs gingivitis purpura and other hemorrhagic symptoms are the classic manifestations. Undeveloped cases are supposedly common and often mistaken for rheumatism.<sup>1292, 1274</sup> Infantile scurvy is clinically characterized by pallor a worried facial expression drawn up legs in bed crying when handled pain in the legs subperiosteal hemorrhages especially in the epiphyseal region and gingivitis with bleeding if the child already has teeth. Anorexia loss of weight susceptibility to infection fever intestinal disorders hematuria and epistaxis are other symptoms. Urbach<sup>129</sup> considers the saturation test for vitamin A deficiency as much more valuable than single determinations of the vitamin A content of blood plasma and urine. This test is based on the observation that the ascorbic acid levels in blood and urine fail to rise substantially and for considerable time in a vitamin A depleted organism after the intravenous injection of 500 mg. of ascorbic acid. In the normal 40 per cent of the injected vitamin is excreted within four hours while in scurvy the excretion is trifling 20 per cent at the most. The diagnosis is helped by the positive tourniquet (Leede-Rumpel) test or a similar method<sup>1297</sup> for testing the fragility of the capillaries. Bleeding and coagulation times as well as blood platelet count are normal.

The blood picture is normal except for a moderate anemia.

The dermatomes of scurvy are significant, though not specific. The follicular lightly papular dull red hemorrhagic rash occurs early in the course of clinical scurvy. Later many of these papules show pronounced intrafollicular keratosis. The rash is symmetrical and occupies predominantly the extensor surfaces of the extremities particularly of the lower legs and the hairy region of the trunk. The palms and soles the face and the scalp remain free.<sup>1221, 1217</sup> Some of the follicular lesions are truly petechial without a papular character. Large subcutaneous extravasations occur in the parts which are subject to friction and

<sup>1291</sup>Eddy, W. H. The Avitaminoses, Baltimore, 1937, Williams & Williams Co.

<sup>1297</sup>Göthlin, H. F. Method for Determining Strength of the Skin Capillaries. Indirect Estimation of the Individual Vitamin C Standard. *J. Lab. & Clin. Med.* 19: 4 4-490, 1933.

trauma such as the popliteal areas and the scalp. Extravasation beneath the conjunctivae also occurs. These dermadromes are more common in infantile scurvy (Möller-Barlow disease).

The papulo-hemorrhagic, keratotic and follicular rash in scurvy has for a long time been known under various other names, like lichen scorbuticus<sup>277</sup> lichen pilaris or scorbutic gooseflesh<sup>278</sup>. The First World War gave the opportunity for new observations of scurvy on a large scale. In some series the papulokeratotic rash was present in 87 per cent.<sup>222</sup> The follicular keratoses often affected almost all follicles especially of the anterior aspects of the legs so that a grater-like surface resulted. Microscopic features of the scorbutic skin lesions are capillary congestion, interstitial hemorrhage and edema without inflammatory infiltrate. The follicle contains a plug formed of the remnant of the hair and keratotic material. The hair roots are not destroyed.

The follicular lesions in scurvy (Whitfield after Wiltshire<sup>229</sup>) have much clinical resemblance to those in vitamin A deficiency. However the vascular factor which is so pronounced in scurvy is lacking in phrynoderma. Scheer and Keil<sup>279</sup> therefore believe that the follicular keratoses in scurvy are not due to a multiple deficiency. In *experimental rikettsia* A deficiency in man follicular keratotic papules and perifollicular petechiae were among the first symptoms.<sup>280</sup> Echinomoses and gingivitis followed.

*Hyperpigmentation* in scurvy has been observed<sup>237</sup> although it is not yet sure whether it is due only to hemosiderin from the hemorrhagic disease or also to the increased melanin production under the influence of vitamin C deficiency. Ascorbic acid is able at least under experimental conditions to prevent melanin formation (von Szent-Györgyi after Schaaff<sup>281</sup>). In the human skin melanin occurs associated with vitamin C.<sup>187</sup>

*Gingivitis* in scurvy being an early signal is of great significance. The gums are swollen and bleeding; the papillae being enlarged. In small children the teeth may become submerged under the swollen gingiva. If the scurvy lasts longer the teeth may fall out and the alveolus may become necrotic. It has often been stated that scorbutic gingivitis does not develop in an edentulous mouth.

*The healing of wounds* is greatly impaired in scurvy<sup>270, 292</sup> at least in part due to the disturbed production of intercellular substances.

Untreated and fully developed scurvy is a disease with a high mortality. However if treatment with 200-300 mg. of vitamin C is administered daily either orally or parenterally together with a full diet surprising recovery may be seen. Gordon and Sevringhaus<sup>287</sup> state that in all the field of medicine there is probably no more dramatic or gratifying result from a therapeutic measure than that which occurs when a patient with scurvy is given an adequate amount of ascorbic acid.

<sup>277</sup>Jeunier, S. *Manifestationen bei inneren Krankheiten*, Berlin, 1893. A. Hirschwald.

<sup>278</sup>Achery, M. and Keil, H. Follicular Lesions in Vitamin A and C Deficiencies. *Arch. Dermat. & Syph.* 39: 177-183, 1924.

<sup>279</sup>Whitaker, H. Hyperkeratosis of the Hair Follicles in Scurvy. *Lancet* 2: 564, 1919.

<sup>280</sup>Crandon, J. H. Lund, C. C. and Dill, H. B. *Experimental Human Scurvy*. New England J. Med. 222: 332-360, 1940.

<sup>281</sup>Barthelt, M. K., Jones, C. M., and Ryan, A. K. Vitamin C and Wound Healing. *Experimental Wounds in Guinea Pigs*. New England J. Med. 228: 469-473, 1942.

No relationship between the level of vitamin C in the blood and the development of a variety of skin diseases altogether 181 cases was found<sup>222</sup> and no curative effect was noticed.<sup>224</sup> Effects on *colloid milium*<sup>226</sup> and on *toxicodermas* from arsenamine<sup>224</sup> mercury<sup>227</sup> gold<sup>228</sup> have been reported. Some evidence is available that vitamin C exerts a detoxifying influence on arsenamine treatment and thus may be able to prevent toxic reactions.<sup>229</sup>

<sup>222</sup>Lacey W F and Talbot J H. Role of Vitamin C in C's arsenic Dermatitis, Arch. Dermat. & Syph. 41 837-863, 1910.

<sup>224</sup>Lincoln, P. and Branstetter, P. Vitamin C and Skin Disease. Arch. Dermat.-venereol. 38 676 1929. Abstr. Arch. Dermat. & Syph. 48: 209.

<sup>226</sup>W y R C. Collloid Milium. Vitamin Deficiency? Arch. Dermat. & Syph. 48 1145-1155, 1943.

<sup>228</sup>Dalmer I. Dermal Lesion Effect of L-Ascorbic Acid (Vitamin C). Curative Effect in Salvarsan and Gold Intolerance. Ann. de dermat. et. syph. 61 420-437 1935.

<sup>227</sup>Takahashi, K. and Kuroki, S. Klinische Anwendung von Vitamin C gegen verschiedene Dermatosen. Jap. J. Dermat. & Syph. 42 133, 1937. SW 68 23.

<sup>229</sup>Baigore O. Vitamin and Disorders of the Skin. Brit. J. Derm. 54 163 1942.

<sup>223</sup>Lehler A. D. Relation of Blood Ascorbic Acid Clearance. Arsenical Intolerance in Syphilotherapy. Brit. J. Dermat. 53 134-169 1943.

## CHAPTER XXII

# DISORDERS OF THE BLOOD AND BLOOD FORMING ORGANS

### (Lymphoblastomas and Allied Disorders)

Leukemia lymphosarcoma Hodgkin's disease, mycosis fungoides, and the subvarieties of these disorders are now—at least in America—commonly grouped together under the name of lymphoblastomas.<sup>220</sup> This term which is not much used in other countries is based on the conception that all these diseases have tumorlike features and that they are related by a common characteristic cell the lymphoblast or a derivative of this cell. A great number of transitional cases have been described to corroborate the close relationship<sup>220-222</sup> The neoplastic features are found in the continuous and uncontrolled proliferation of cells, which tend to differentiate like their cells of origin. The proliferation is infiltrating and is devoid of an orderly structural arrangement. No cause is known. The course is invariably fatal no certain phenomena of immunity or protection are known.<sup>221</sup> Heredity plays a role.<sup>222</sup>

Other authors<sup>220</sup> produced some evidence for the infectious nature of the group. Spread of the disease from a portal in the lymphatic tissues of the gastrointestinal and respiratory tract inflammation necrosis, fever and some experimental facts can be interpreted in favor of an infectious, possibly virus<sup>222</sup> etiology. Possibly in future a conception of infectious neoplasm will evolve.

The term lymphoblastoma as a generic term has been accepted by authors who do not approve of the merging of the entities in question since they consider the differentiating characteristics of greater importance.<sup>221</sup>

### Leukemia<sup>220, 222, 223</sup>

Leukemia is a fatal disease of unknown etiology primarily involving the blood-forming organs i.e. the bone marrow the spleen the lymphatic nodes

<sup>220</sup>Klein, H. L. Lymphoblastomas. Their Interrelationships, Arch. Dermat. & Syph. 19: 532-594, 1927.

<sup>221</sup>Kruschkear, E. D. Hodgkin Disease. Present Status, University of Wisconsin Symposium on Blood, pp. 145-169, 1929.

<sup>222</sup>Warkin, A. R. Relationships of Hodgkin Disease, Aleukemic and Leukemic Lymphoblastoma and Mycosis fungoides, Ann. Surg. 92: 182-191, 1930.

<sup>223</sup>Fraser, J. F. Mycosis fungoides as Variety of Lymphosarcoma, Arch. Dermat. & Syph. 11: 451-458, 1925.

<sup>224</sup>Fraser, J. F. Mycosis fungoides, Its Relation to Leukemia and Lymphosarcoma, Arch. Dermat. & Syph. 11: 14-22, 1925.

<sup>225</sup>Wile, C. J. and Stiles, F. J. Clinical Metastases in Lymphoblastomas, J. A. M. A. 194: 523-527, 1925.

<sup>226</sup>Apfel, K. Die Leukämien als Neoplasmen, Virchows Arch. B. 20: 1-99, 1927.

<sup>227</sup>MacDermott, H. B. Principles of Pathologic Histology, Philadelphia, 1914. W. B. Saunders Co.

<sup>228</sup>Wiley, M. Heredity of Leukemia (in Milk), Am. J. Cancer 22: 196-199, 1933.

<sup>229</sup>Klein, H. L. Cutaneous Lymphoblastomas, Chicago 2: 868-878, 1934.

<sup>230</sup>Forsaker, O. K. Leukemia and Allied Disorders, New York, 1933. The Macmillan Co.

<sup>231</sup>Ormsby, O. S. and Finerman, C. W. Mycosis fungoides, Arch. Dermat. & Syph. 27: 631-642, 1923.

<sup>232</sup>Haden, R. L. Hematology, Philadelphia, 1929, Lea & Febiger.

<sup>233</sup>Kossmick, M. and Harris, W. Leukemia, Diagnosis and Treatment, J. A. M. A. 194: 793-796, 1933.



and the reticuloendothelial cell. It is characterized by widespread rapid and disorderly proliferation of the white blood cells and their precursors. Almost without exception either during the entire course or in some phase of the disease the white blood count is high sometimes very high. The appearance of immature leukocytes in the blood often in very large numbers is particularly significant. This proliferation of white cells almost always involves only one of the three types the lymphocytes the granulocytes or the monocytes. This is surprising considering the adjacency of the mother cell in the bone marrow and in other organs. The resulting three main types of leukemia the lymphoid the myeloid and the monocytic are clinically quite different. Generalized enlargement of the lymph nodes is typical of lymphoid leukemia but some lymphadenopathy may be present in the other types. The spleen is usually enlarged the very large sizes being found in myeloid leukemia. In monocytic leukemia gangrenous and hemorrhagic lesions of the mucous membranes often dominate the picture. Weakness, dyspnea fever and anemia occur in all types. A hemorrhagic tendency is an early and common feature in all types. The metabolic rate is frequently increased. In two out of three cases the disease takes a chronic course over years with or without remissions. The acute disease ends fatally in a few weeks or months, often with hemorrhagic and mucosal symptoms. Acute course is known to occur in any of the three types. Approximately one half of the myelocytic and of the monocytic cases but only one fourth of the lymphocytic cases are acute.<sup>304</sup>

The leukemias are relatively rare diseases. They constitute a little more than one-half per cent of the necropsy diagnoses in a large American series (Ikeda after Forkner<sup>305</sup>) with about two cases of lymphoid leukemia to one case of myeloid leukemia. This ratio among the necropsies differs materially from that of hospital admissions. Among 455 cases of leukemia treated in Mount Sinai Hospital in New York roughly 66 per cent were myeloid 28 per cent lymphoid and 1.5 per cent monocytic. In Denmark roughly one out of 50,000 persons dies of leukemia per year (Nielsen after Forkner<sup>306</sup>). No age is exempt but the fourth decade of life has the largest incidence. The male patients outnumber the females two to one.<sup>304</sup>

**Dermadromes Especially of Lymphatic Leukemia.**—Cutaneous lesions occur in all types of leukemia. It is customary to distinguish between specific skin lesions which histologically consist of the same cell which are characteristic of the blood in the case in question and nonspecific dermatoses which are often seen in leukemia but do not contain leukemic elements.

The border line is not very sharp since originally nonspecific lesions may finally become pervaded by the leukemia cells. Even grossly normal skin may prove to harbour specific infiltration. The nonspecific group is often called leukemids<sup>324b</sup> or just *ids*. The term leukemid has become misleading since

<sup>304</sup>Friedmann, A. B. and Meyer, L. M. Observations on Over 100 Cases of Myelogenous and Lymphatic Leukemia. *Radiology* 31: 311-343 1948.

<sup>324b</sup>Andry, C. Sur les leucémides, *Bull. Soc. franç. de dermat. et syph.* 23: 118-121 1902.

in analogy to the "ids" in infections it suggests the specific and not the non-specific type e.g. syphilids trichophytids, etc. (see discussion to Swietzer<sup>3267</sup>) The term "accompanying dermatoses" (Hautbegleitserscheinungen<sup>3268</sup>) has not found approval in the Anglo-Saxon literature. The adjective, toxic, has also been used to characterize these dermatoses. It implies an etiology which has not been proved. It seems best to speak of specific and nonspecific dermatomes. There is no dermatome which in a clinical sense is absolutely characteristic of one or the other types of leukemia. The majority of published cases of skin lesions belongs to the chronic lymphoid leukemia.<sup>3267</sup> However in an analysis of the cutaneous aspect of 160 cases of leukemia<sup>3269</sup> the incidence was about equal in both main types. Specific infiltrations were more common in lymphoid leukemia (8.3 versus 5.5 per cent). The cutaneous involvement in monocytic leukemia seems very high (75 per cent) but only small numbers are so far available. The diagnostic difficulties in skin leukemia are considerably increased by the experience that the cases with leukemic skin manifestations are frequently subleukemic or aleukemic in the blood.<sup>3267</sup> They often show a leukemic blood only in late stages of the disease. Another difficulty may be created by lymphocytomas. These are infiltrations or tumors which histologically resemble leukemia but remain localized.

**Non-Specific Dermatomes.**—These are variable. In their monograph Arst and Fuhs<sup>3270</sup> mention dermatitis, eczema, erythema exudativum multiforme, urticaria, purpura and bullous and rupial eruptions. This coincides with Nanta's remark that there are so many combinations in this group that if one would like to go into grouping every single observation could represent a type of its own. The incidence is probably higher than fifty per cent, minor skin lesions often passing unnoticed or at least unrecorded in the medical wards. Pruritus for instance sometimes without any visible skin changes, which seems to be the most common symptom, was recorded only in three per cent of the leukemia cases of Epstein and MacEachern.<sup>3271</sup> Most authors agree that severe itching alone or in connection with visible rashes is a frequent symptom.<sup>3272</sup>

Purpura of varying degrees is also common in leukemia. In large series<sup>3267, 3273</sup> it exceeds the other leukemic rashes. This is not surprising in view of the thrombopenia and hemorrhagic tendency in the leukemias. Chronic urticaria<sup>3274-3275</sup> has quite often been described. It is related to Buschke's prurigo lymphatica. This is a violently itching widespread not too dense eruption of small papules, which soon become scratched and crusty or impetiginous. The lesions may form

<sup>3267</sup>Swietzer, S. K. Leukemia. Arch. Dermat. & Syph. 29: 1082-1083, 1909.

<sup>3268</sup>Oetters, H. Zur Leukämie der Haut. Med. Klin. 28: 873-877, 404-406, 1937.

<sup>3269</sup>Epstein, E. and MacEachern, K. Dermatologic Manifestations of the Lymphoblastoma-Leukemia Group. Arch. Int. Med. 69: 867-873, 1937.

<sup>3270</sup>Arst, L. and Fuhs, H. Hauterkrankungen bei Leukosen und Leukoblastosen sowie verwandten Zuständen. Handb. d. H. Gk. 8, 1 1929.

<sup>3271</sup>Corsham, T. and Murphy, E. L. Lymphatic Leukemia (Chronic). Leukemia Orits. Arch. Dermat. & Syph. 28: 643-645, 1937.

<sup>3272</sup>Cavanagh, J. M. Lymphoblastoma. Arch. Dermat. & Syph. 23: 227, 1921.

<sup>3273</sup>Schreiner, C. H. Ein Fall von chronischer lymphatischer Leukämie ohne Mfz oder Mandelgeschwulst, aber mit Urticaria. Med. Rev. 83: 420-422, 1936; Zbl. 23: 543.

<sup>3274</sup>Grand, A. Osservazioni cliniche leucemico. Arch. Ital. di dermat. sif. 7: 897-911, 1921; Zbl. 47: 82.

small erosions and ulcers which leave pigmented spots and streaks. Thus a mottled melanoderma may ensue which resembles the so-called vagabond's skin. The frequent loss of body hair in this stage is not only due to the rubbing off but also to a beginning specific infiltration around the hair follicles.<sup>101</sup> Total alopecia has been observed. The histologic picture is as a rule not a typical leukemic one but surprising specific findings have become known demonstrating that there is no sharp borderline between the specific and nonspecific dermatromes.<sup>101 102</sup> The same is true of the herpes zoster which occurs quite often in the course of leukemia.<sup>103</sup> While the zoster may take a normal course its scars may later become the sites of specific leukemic infiltrations.<sup>104 105</sup> Such provocations of specific leukemic lesions by local inflammation or trauma interpreted as Koebner's phenomenon have been observed in many cases after local trauma like insect bites, burns, cupping, piercing of the earlobe, pinching of the ear and other local mechanical injuries.<sup>106</sup> Aberrant or generalized zoster eruptions which are quite rare seem to occur more frequently in leukemia.<sup>107 108 109</sup> The rare connection of zoster and chicken pox in adults, and also the varicelliform eruptions (H. R. Foerster in discussion to Barney<sup>100 109</sup>) have been observed several times in leukemic patients. The generalization of zoster seems to occur especially in persons whose resistance has been weakened by disease or age.<sup>110 111</sup> Evidence of involvement of the corresponding spinal ganglion by hemorrhage or leukemic infiltration is on record.<sup>112</sup> Some of the zoster eruptions in leukemia may have been caused by arsenical

**Specific Leukemic Dermatromes.**—Specific leukemic dermatromes appear in several types which notwithstanding their different clinical aspect have

- <sup>100</sup>Vaia, A. Les troubles de l'appareil hématopoïétique (Hématodermes). Nouvelle Pratique Dermat. ologique vol. 5 pp. 521-591.
- <sup>101</sup>Artz, L. Leukämische Lymphadenome. Zbl. 48: 57.
- <sup>102</sup>Bertraciel, G. Leber einer sehr früh beginnenden II. (erkrankung (Beispiel im Verlauf einer chronischen leukämischen Lymphadenose. Dermat. Wchnsch. 96: 741-744, 1921.
- <sup>103</sup>Craut, L. P. and Haasman, C. D. A. Not on the Occurrence of Herpes Zoster in Hodgkin's Disease. Lymphomatoses and the Leukemias. Am. J. Cancer 16: 502-511, 1922.
- <sup>104</sup>Jadassohn, J. II. Leukämie in Zoster-Ringen. Zbl. 52: 17.
- <sup>105</sup>Jadassohn, J. Herpes Zoster and arborescens Eruption bei lymphatischer Leukämie. Zbl. 50: 12.
- <sup>106</sup>Maile, H. Zoster und Leukämie. Provocation leukämischer Infekt in der Haut. Arch. f. Dermat. u. Syph. 159: 254-25, 1919.
- <sup>107</sup>Ka. II. Zoster bei Leukämie. Arch. f. Dermat. u. Syph. 164: 461-464, 1922.
- <sup>108</sup>Ferrero, Jacques, J. Herpes zoster generalisé en bei Leukämie. Arch. f. Dermat. u. Syph. 170: 285-304, 1927.
- <sup>109</sup>Gorou, H. and Jacob, H. Subleukämische Lymphadenome mit sehr Herpes Zoster generalisation. Zbl. 52: 84, 1920.
- <sup>110</sup>Darney, R. E. Leukemia with Resembling Herpes Zoster. Arch. Dermat. & Syph. 25: 1750-1151, 1922.
- <sup>111</sup>Darney, R. E. Zosteriform Leukemia. With. Arch. Dermat. & Syph. 27: 324-348, 1924.
- <sup>112</sup>Parade, O. W. and Vogt, H. Zur Frage der Haut leukämie. Deutsches Arch. f. klin. Med. 106: 361, 1910.
- <sup>113</sup>Haas, K. Zoster generalisatio bei lymphatischer Leukämie. Dermat. Wchnsch. 96: 1819-1820, 1923.
- <sup>114</sup>Horton, R. L. and Leary, P. A. Herpes Zoster Generalisatus Associated With Chronic Lymphatic Leukemia. Arch. Dermat. & Syph. 82: 283-285, 1918.
- <sup>115</sup>Lutz, W. Klin. Dermat. in Relation to General Organism. Review of Literature. Dermatologica 23: 177-180, 1911.
- <sup>116</sup>Philadelpy, A. and Hadbofer, L. Varicellen bei leukämischer Lymphadenose. Arch. f. Dermat. u. Syph. 100: 512-518, 1921.
- <sup>117</sup>Freund, H. Zoster und Leukämie. Arch. f. Dermat. u. Syph. 164: 478-480, 1924.

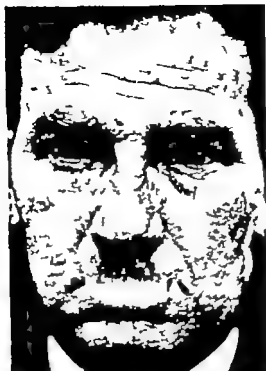


Fig. 203 — Lymphatic leukemia. Specific papular eruption. (Courtesy Dr. M. Jenner.)

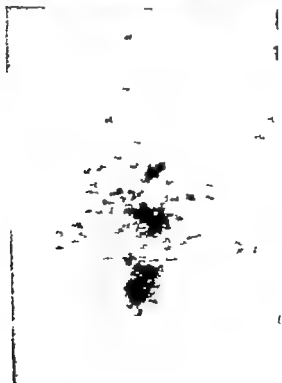


Fig. 204 — L. lymphatic leukemia. Erythematous eruption. (Courtesy Dr. M. Jenner.)

is common histopathology the leukemic infiltration. The rarest of the specific leukemic involvements of the skin is the generalized papular rash which has great similarity to a secondary syphilitic exanthema. The dense<sup>329</sup> eruption of small red mostly follicular papules favors the trunk especially the hips leaving the face and the limbs relatively free. Considering its great rarity the diagnosis



Fig. 307. Specific papular eruption in lymphatic leukemia. (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)

of leukemia will hardly be made from the rash alone. But after exclusion of syphilis and other papular exanthemas, e.g. drug eruptions leukemia should be considered.<sup>329-333</sup> This diagnosis will be much easier if the papules tend to coalesce and form plaques or if some papules reach tumor size. Such cases of tumors arising from beds of papules link the papular type of cutaneous leukemia with the leukemic tumors. Another transition is the furunculosis-resembling rash of large not very distinct papules of moderately dense distribution.<sup>31</sup>

The cutaneous tumors in leukemia<sup>339-421</sup> have been seen in sizes varying from a pinhead to a large potato. They are oval or round mostly raised. If they are

<sup>329</sup>Arri, L. Prurigo Lymphatica, Ebl. 81: 11.

<sup>331</sup>Rosenowsky. Lymphatische Leukämie mit spezifisch papulösem Exanthem und bullöser Eruption, Ebl. 81: 64.

confluent the lines of coalescence are sometimes recognizable by deep linear grooves. Their color may be red bluish purple brown even almost black. Under diascopic pressure they appear brown. The skin over the tumors may be extended glossy atrophic with some telangiectases or scaly. The tumors are usually movable. The small tumors are quite hard. The large growths are often described as soft, less often as having the elastic hardness of cartilage. The tendency to spontaneous regression either by central necrosis or healing with atrophy is small (Freudenthal after Gottron<sup>207</sup>) also<sup>208</sup>. They are almost always painless. The tumors may appear in any region of the body surfaces



Fig. 304—Lymphatic leukemic tumors (Courtesy D. M. Josselyn)

but they have a definite affinity to the soft area of the face i. e. the eyelids, the lips, the nose, the cheeks, and the ear lobes. There is a certain tendency to symmetric development. Such symmetric tumors may create the most grotesque disfigurement of the human face known to medicine. In such rare but well known cases large bluish bulges hang over the eyes and cheeks obstructing the vision. The nose resembles a proboscis, the ear lobules may be pendulous and elongated. In other cases the tumefaction is more diffuse over the face resulting in a *facies leonina* not unlike leprosy. The scalp may also be involved. The penis and prepuce sometimes become the site of leukemic tumors which may seriously interfere with micturition. The nipples soft area too have several times been described as a characteristic site of leukemic tumors.<sup>209-210</sup>

<sup>207</sup> Bachel, P. E. Leukemia, Arch. Dermat. & Syph. 18: 600, 1923.

<sup>208</sup> Freudenthal, J. M. Circumscribed Leukemia Cutis, Arch. Dermat. & Syph. 32: 141, 1925.

<sup>209</sup> Whitehouse—Myelogenous Leukemia, Arch. Dermat. & Syph. 18: 798-800, 1923.

The *mucous membranes* of the mouth pharynx larynx nose and eyes may also become involved. Oral lesion of this kind are described as nodular or diffuse infiltration. A picture of a patient of Milian<sup>221</sup> shows a lobulated gyrate tumor involving the whole soft palate and covered with petechiae. Such infiltrations of the soft palate have been seen several times<sup>222</sup>. Connor describes a similar case in a Negro. There were large flat granulomatous masses practically covering the buccal surfaces on both sides. Smaller tumors were located on the soft palate and on the gums. The masses were dull red the edges overhanging the bases sessile. There was some superficial ulceration in this case but the lack of ulceration is emphasized in other cases. In other instances<sup>223</sup> the infiltrations were smooth and multiple scattered over the entire mucosa of the upper air passages from the lips down to the larynx. In one case a tumor of the epiglottis accompanied by skin tumors proved to be of lymphocytic origin<sup>224</sup>.

Tumors have been observed in all ages including a seven months old baby<sup>225</sup> a three year-old boy<sup>226</sup> and very old people.

The tumors often grow slowly or remain stationary over long periods even as long as thirteen years.

In some cases the appearance<sup>227</sup> of cutaneous tumors coincides with a change of a chronic course to an acute phase of leukemia with more numerous immature cells in the blood<sup>228</sup>.

The diagnosis of the leukemic tumors is easy in fully developed cases. But difficulties which can only be overcome by repeated biopsies may arise if there is only one small nodule<sup>229</sup> or if the lesion resembles other tumors e.g. ulcerated epithelioma<sup>230 231</sup> melanoma<sup>232 233</sup> hemangioma<sup>234</sup> or neurogenic sarcoma (author's case). Blood count and biopsy will finally assure the diagnosis but it should be remembered that large tumors of the skin may be found in an aleukemic phase of the disease<sup>235</sup>.

*Generalized Exfoliative Erythroderma*. This complication of leukemia is very rare. Epstein and MacEachern<sup>236</sup> saw one case in 60 cases of chronic lymphoid leukemia and not a single case in 90 cases of myeloid leukemia. It is about five times rarer than the other dermatomes of lymphoid leukemia.

- <sup>221</sup>Milian J. *Leucémie maligne*. Arch. Derm. & Syph. 19 843-8 & 1939.  
<sup>222</sup>Marx H. *Leucämie cutis mit Beteiligung des Rachens und des Kehlkopfes*. Ztschr. f. Laryng. Rhin. 191 207-208 1930.  
<sup>223</sup>Al. Caffery. *Lymphoma*. Arch. Dermat. & Syph. 19 843-8 & 1939.  
<sup>224</sup>Malting-Nichols J. B. *Ein Fall von Hämorrhagischer und myeloide Reaktion im Häm. Knoch. nach gonorr. Inf.* 719-720 1930. Ztschr. 33 435.  
<sup>225</sup>Benson H. *Leukemia*. Little Press. Ro. New Med. 33 1031 1032. 1930.  
<sup>226</sup>Janlin-Wall P. and Jack-Wall P. *Leucämie cutis*. Arch. Derm. & Syph. 19 843-8 & 1939.  
<sup>227</sup>Zelmer E. F. and Carr M. E. *Lymphatic Leukemia of the Skin*. Arch. Dermat. & Syph. 36 522 1932.  
<sup>228</sup>Bauschke A. *Lymphatische Leukämie*. Ztschr. 41 295.  
<sup>229</sup>White C. J. *Leukemia cutis, Resembling Epithelioma*. Arch. Dermat. & Syph. 36 431 1932.  
<sup>230</sup>Gray A. M. H. *Leukemia cutis*. Proc. Roy. Soc. Med. 33 1841 1842 1930.  
<sup>231</sup>Rosenberg A. *Lymphatic Leukemia*. Arch. Dermat. & Syph. 33 487 1931.  
<sup>232</sup>Thomsen B. *Lymphatic Leukemia*. Arch. Dermat. & Syph. 29 556 1929.  
<sup>233</sup>Shimmerman E. F. and Curtis, R. C. *Aleukemic Myeloid with Cutaneous Nodules*. Arch. Dermat. & Syph. 33 694-699 1930.

The condition may precede the blood changes for years<sup>2224</sup> or it may develop in any stage of the leukemic process. It may develop secondarily to a specific papular rash or specific nodules,<sup>2225, 2226</sup> or nodules or tumors may follow the diffuse reddening of the skin.<sup>2227</sup> In other cases the universal involvement of the skin was ushered in by swelling and erythema of some regions—mostly the groin and armpits<sup>2224, 2225</sup> or by bullous eruptions suggesting pemphigus.<sup>2228</sup> In some instances excessive perspiration was an initial symptom.<sup>2227</sup> Pruritus was almost always severe and remained so throughout the course of the disease. The variety of pictures seen in the initial stage of the disorder is in remarkable contrast to the uniformity of the later stages.

The entire body surface is red—sometimes bright red—sometimes dusky or purplish. The skin is often thick and leathery—hardly pliable. While the small wrinkles are mostly flattened, the large folds are the more deepened. The loss of pliability expresses itself in painful fissures especially on the hands. The exfoliation varies from slight branny scaling to the shedding of large sheets of dry epidermis. In some cases vesicles, crusts and oozing create the impression of a generalized eczema. Nodules or plaques are sometimes found in the erythroderma. The axillary and pubic hair is shed early or rubbed off—the hair of the bearded area and of the scalp follow.<sup>2229, 2230, 2231</sup> The ground off concave edges of the nails and their glossy surfaces, tell of constant rubbing and scratching. Later on they are often dystrophic, thickened, opaque, brittle and discolored.

The superficial lymphatic nodes are all swollen—the lack of axillary and pubic hair making them more visible. The patient is very uncomfortable. The rashes, the pruritus, the ectropion which usually develops, complicating pyodermic infections, chilliness and the weakness and depression caused by the severe disease create a horrible syndrome of suffering. The course may drag on over many years. In the later stages the infiltrated skin may become atrophic.<sup>2232</sup> Leukemic erythroderma is usually not influenced by any treatment including radiation.

The fatal outcome is frequently precipitated by bronchopneumonia.

<sup>2224</sup>Cuvier, J. S. and Fruto, J. O. Erythrodermie Form der akuten Leukämie. *Acta dermato-ol.* 19: 316-323 226 1937. *Id.* 23: 70.

<sup>2225</sup>Fellmann, J. Erythroderma leucæmicum als chronischer lymphatischer Leukämie mit Knochen nach Röntgenbestrahlung ex. iectio. *Cervot. bel.* 77: 264-267 1933. *Id.* 43: 459.

<sup>2226</sup>Schall, E. Erythroderma lymphæ leucæmicæ. *Plakm. Moll. Sc. Region. Soc. Ital. Dermat.* pp. 116-118. 1932.

<sup>2227</sup>Dalme, H. and De Marval, L. Ueber einen Fall von Erythrodermie und akuter lymphatischer Leukämie. *Dermat. Wchnsch.* 109: 11 1180-1187.

<sup>2228</sup>Nicholson, H. E. Leukæmia Cutis. *Arch. Dermat. & Syph.* 23: 148-149, 1930.

<sup>2229</sup>McCarthy, P. P. Raynaud Disease (Possibly Due to Chronic Arterio Sclerosis). *Arch. Dermat. & Syph.* 23: 787-794, 1931.

<sup>2230</sup>Margaret, J. Rimbad, P. and Roche, J. Erythrodermie écoustique. In: *Manifesta cliniques initiales et évènements quelques temps évènements d'une leucémie diffractée primordiale et d'opération sub-algus*. Bull. Soc. franç. de Dermat. et Syph. 42: 1933- 519, 1933.

<sup>2231</sup>MacCombie, H. Leukæmic Erythroderma. *Proc. Roy. Soc. Med.* 23: 1171-1174, 1932.

<sup>2232</sup>Amersbach, V. Chronische lymphatische Leukämie mit Lymphoma der Haut. *Berch. Arch. f. d. ges. Med.* 36: 413-417 1934. *Id.* 38: 296.

<sup>2233</sup>Theodoresco, R. Sur un cas d'érythrodermie leucémique. *Bull. Soc. roum. Dermat.* 1: 61-64 1929. *Id.* 3: 323.



**Chronic Myeloid Leukemia**—Skin manifestations of chronic myeloid leukemia being much rarer than those in lymphoid leukemia are not yet well enough known to insure a definite type. Hardly more than fifty cases have been published. All the dermatomes observed in chronic lymphatic leukemia have been seen in the chronic myeloid type too. Nonspecific hemorrhagic,<sup>300</sup>



Fig. 308



Fig. 310

Fig. 308—Chronic myeloid leukemia. Specific cutaneous tumors. (From Paul, J. T. and Lissard, L. R. Arch. Dermat. 1912.)

Fig. 310—Chronic myeloid leukemia. (From Paul, J. T. and Lissard, L. R. Arch. Dermat., 1912.)

urticarial pruriginous rashes<sup>301,302</sup> as well as infiltrations, plaques,<sup>303</sup> and tumors are known.<sup>304</sup> The impression prevails that there is less tendency for the tumors to develop in the soft areas especially in those of the face. The facies leonina which is so striking in some cases of lymphoid leukemia has not yet become known in myeloid leukemia. The tumors seem to occur more frequently on the trunk.<sup>305,306</sup> The extremities have only occasionally been found to be involved.

<sup>300</sup>Martensstein, H. Multiple Hautblutungen bei myelischer Leukämie. *Id.* 35 96 1937.  
<sup>301</sup>Nekam, L. Les manifestations cutanées de la leucémie myéloïde chronique. *Bull. Soc. franç. de dermat. et syph.* 46 1236-1254 1937.

<sup>302</sup>Haden, R. L. Leukemia Cutis (Myeloblastic). *Arch. Dermat. & Syph.* 27 870-871, 1933.  
<sup>303</sup>Paul, J. T. and Lissard, R. R. Specific Cutaneous Lesions in Chronic Leukemia. *Arch. Dermat. & Syph.* 45 897-906, 1912.



mycosis fungoides<sup>326, 327</sup>. Shotty, papular<sup>327</sup> nodular or tumorous discrete or coalescent eruptions have become known<sup>327</sup>. The lesions may be either superficial or deep seated creating sarcoïd pictures. Their development seems to be faster and their tendency to spontaneous regression more marked than in the other leukemic tumors. Ulceration<sup>327</sup> is considered ominous.<sup>32</sup> As in the other leukemias the cutaneous changes may precede accompany or follow the



Fig 312 — Monocytic leukemia. (Courtesy Division of Dermatology Department of Medicine University of Chicago.)

blood changes. The dermatological diagnosis of monocytic leukemia can only be established by biopsy and in connection with other clinical findings<sup>327</sup> since the cutaneous picture may resemble all other lymphoblastomas.

<sup>326</sup>Loveman, A. B. Monocytic Leukemia. *Cutis*, South 31: 29: 337-354, 1976.

<sup>327</sup>Montgomery R. and Wilkins, C. H. Exfoliative Dermatitis as Manifestation of Monocytic Leukemia. *Schilling Minn Med J* 31: 636-641, 1939.

<sup>328</sup>Mierer, A. T. The Dermatoses of Monocytic Leukemia. *Arch. Dermat. & Syph* 31: 613-633, 1933.

<sup>329</sup>Freeman, H. E. and Koletsky S. Cutaneous Lesions in Monocytic Leukemia, 2 Cases. *Arch. Dermat. & Syph* 48: 215-240, 1939.

<sup>330</sup>Lynch, F. W. Cutaneous Lesions Associated With Monocytic Leukemia and Erythroid-Endothelioid, *Arch. Dermat. & Syph* 34: 775-798, 1936.

**Chloroma.**—In contrast to the earlier literature chloroma is now considered a variant of myeloid leukemia originating from the marrow especially of the cranial bones, and taking the course of a highly malignant tumor. The name (green tumor) characterizes the green color of the lesions produced by a lipid, probably iron-containing substance. Two main clinical types of chloroma occur.<sup>374</sup> In the juvenile cases a rapidly growing orbital tumor produces exophthalmus and finally profound proptosis. Cranial tumefaction with a great variety of symptoms, lymphadenopathy, gross involvement of other bones and severe anemia follow. In the much rarer adult type the course resembles acute leukemia complicated by gross bony involvement.

Since the arrival of the modern methods of hematology myeloid leukemia has been found to be present almost constantly. Autopsy reveals green foci of myeloid tissue throughout the body.

Severe anemia with a green hue and petechial purpura and varying macular or papular rashes<sup>375</sup> and tumors<sup>376</sup> have been described mostly in children. Dense nodular greenish rashes in adults are known. Similar to other acute leukemias, ulcerative gingivitis and early bleeding infiltrations of the base of the tongue and of the tonsils occur. In contrast to the oral lesions of other leukemias these lesions are green in color.



Fig. 818.—Ecchymoses in acute lymphatic leukemia.

**Acute Leukemia.**—Acute leukemia occurs about half as often as chronic leukemia and four out of five acute cases belong to the myeloid type.<sup>382</sup> Acute leukemia<sup>378</sup> usually starts with enlarged tonsils, stomatitis and/or upper respiratory infection of more than usual persistence and severity. Hemorrhages from mucous membranes particularly of the nose and gums are an early symptom which persists throughout the disease. Anemia develops rapidly. Splenic

<sup>374</sup>Kandel E A. Chloroma. Arch Int Med 50: 691-701, 1937.

<sup>375</sup>Jordan M, Fox J, A A and Rubenstein R J. Constitutional Leukemia With "Chloroma." Am J Dis Child 56: 222-229, 1930.

<sup>376</sup>Furber C E. Acute Especially Monocytic Leukemia. Arch Int Med 53: 1-24, 1934.

enlargement often causes abdominal tenderness. Due to the increasing hemorrhagic diathesis bronchopneumonia or sepsis death ensues within four weeks or less in 60 per cent of the patients and within eight weeks in 84 per cent.<sup>277</sup> None of 113 cases lived longer than twenty-six weeks.

The white cells, which dominate the blood picture with usually over eighty per cent are uniform and immature mostly myeloblasts less often lymphoblasts or monoblasts. The blood platelets run low and the coagulation and bleeding times are prolonged. The absolute number of leukocytes may be about normal. Leukopenia is common in the early stages.

**Skin and Mucosal Manifestation** — Forkner<sup>278</sup> emphasizes the importance of initial gingivitis as an aid in differentiation of the acute leukemias. It is most marked and diffuse in monocytic leukemia. Here it may extend to the pharynx usually causing ulceration and bleeding. More than in the other types, a diffuse cellulitis is apt to appear about the lesions causing tooth ache and painful acute inflammation in the deeper tissues of the face. The patients are usually first seen by a dentist. If teeth are extracted the bleeding is severe and some times fatal. Deep necroses have followed such extractions. Several authors emphasize the submerging of the teeth in the swollen pale pink soft and tender gums which bleed easily.<sup>279-280</sup> The oral aspect sometimes resembles scurvy. Besides the gingivitis gangrenous punched-out ulcerations in the floor of the mouth occur. The necrotic character of the leukemic infiltration may dominate the changes in the tonsils and the lymphoid tissues of Waldeyer's ring.<sup>281</sup> Noma resembling pictures may ensue.<sup>282,283</sup>

The nonspecific as well as the specific skin manifestations in acute leukemia are essentially the same as in the chronic cases. However the nonspecific eruptions seem to have a purpuric tendency and the specific leukemic lesions show a greater tendency to regressive changes like central softening ulceration necrosis and gangrene. This is illustrated by the observations of severe necroses after minor operations performed on acutely leukemic patients. The deep and wide necrosis after the application of a venocut (Leube and Fleischer after Arzt and Fuhs<sup>284</sup>) belongs here too. The morphology follows the familiar patterns of papular rashes<sup>285-288</sup> nodules tumors plaques and erythroderma.<sup>289</sup>

<sup>277</sup>Farver, H. L. *Acute Leukemia*, Am. J. 51 No. 278: 80-900 1929.

<sup>278</sup>WitzGerald, L. M. *Oral Lesions in Leukemias*, J. Am. M. Soc. 23 421-428, 1942.

<sup>279</sup>Pastermack, J. M., Abbot, G. A. and Werner, B. D. *Leukemic Stomatopathy*, Case of Acute Aleukemic Leukemia, J. Am. Dent. A. 29: 103-1107 1912.

<sup>280</sup>Osmond, E. S. *Monocytic Leukemia*, Report of 6 Cases and Review of 127 Cases, Arch. Int. Med. 199 431-451 1927.

<sup>281</sup>Herr, A. *Klinische Beobachtungen bei der Lymphogranulocytose*, Wien. Arch. f. inn. Med. 24 437-454 1924.

<sup>282</sup>Karl, W. *Acute Myeloblasten-Leukämie*, Zbl. 84 73.

<sup>283</sup>Cohen, I. *Osseous Tumors in Acute Myeloid Leukemia*, Nederl. Hdschr. Geneesk. pp. 1061 1053 1930. Zbl. 84 173.

<sup>284</sup>Kyrtola, T. *Fall von akuter aleukämischer lymphatischer Leukämie mit ausgedehnter spezifischer Hautveränderung*, Festschr. f. Med. B. 1a, pp. 43-49, 1928. Zbl. 28 862, 1929.

<sup>285</sup>Seidberg, F. *Der Katak der Leukemische cutis*, Venerol. 7 23-37 1920. Zbl. 29: 209 1931.

<sup>286</sup>Wassermann, O. *Zur Kasuistik der Erythraemie mit Uebergang in Leukämie*, Klin. Wchnschr. 13: 895-900, 1934.

The histology of leukemic lesions of the skin and mucous membranes is of marked uniformity. There is a more or less dense infiltration of the superficial or deep layers of the cutis, composed of the characteristic leucocytes. The infiltrates often form perivascular sheaths, but in fully developed lesions the accumulation of cells throughout the dermis is so dense that the perivascular arrangement disappears.

## Hodgkin's Disease

### Lymphogranulomatosis (Paltz and Sternberg)

Hodgkin's disease is a chronic disorder of the lymphatic system. It starts in sixty five per cent of the cases with the painless enlargement of cervical lymph nodes. Gradually other groups and finally the entire lymphatic system including the spleen and often the liver become involved. The enlarged lymph nodes may become large tumors which cause severe local symptoms, especially in the mediastinum. Chronic intermittent fever, weakness, loss of weight, cough, edema, diarrhea, anemia and finally cachexia are the usual features. The blood picture is not characteristic but anemia is common. Eosinophilia is present in 20 per cent and leucocytosis is an occasional finding. The course may be rapidly fatal or slowly progressive over one to rarely more than three years. A few instances of survival for much more than ten years are known.

The disease is most common in the third decade of life but no age or race is immune. Three out of five cases are in men.

**Dermadromes.**—The incidence of skin manifestations in lymphogranulomatosis follows, generally the pattern of the other lymphoblastomas. There are nonspecific and specific dermadromes. The former are common and the latter are rare.

**Nonspecific Cutaneous Manifestations.**—The large series vary in their observations on *pruritus* in Hodgkin's disease. Thirty two per cent (Burns after Baum<sup>117</sup>) eighteen per cent<sup>118</sup> six per cent<sup>119</sup> and three per cent (Longcope after Baum<sup>117</sup>) are some of the percentages. Especially in France *pruritus* seems to be considered so common that lack of it prompted publication of three cases.<sup>120</sup> *Pruritus* is often an early symptom which may precede the lymphadenopathy by as long as two years.<sup>121,122</sup> High blood sugar or unexpected high urine sugar

<sup>117</sup>Baum, F. Atypical Cutaneous Symptoms in Lymphogranulomatosis, Arch. f. Dermat. u. Syph. 178: 412-424, 1923.

<sup>118</sup>Burper, E. K., and Lehman, H. P. 54 Cases of Hodgkin's Disease, Arch. Surg. 63: 670-679, 1941.

<sup>119</sup>Oakey, R. S. J. Hodgkin Disease, 52 Cases, Hakertian. Monthly 79: 129-149, 1944.

<sup>120</sup>Foluso, R., Lucchi, G. and Recardier, M. Trois nouveaux cas de lymphogranulomatose maligne sans prurit et sans eosinophilie Sang 3: 330-334, 1929.

<sup>121</sup>Amber, J. V. Hodgkin Disease Arch. Dermat. & Syph. 25: 1149-1150, 1927.

<sup>122</sup>Madden, J. F. Gangrenous Herpes Zoster in Hodgkin's Disease, Arch. Dermat. & Syph. 29: 714, 1929.

enlargement often causes abdominal tenderness. Due to the increasing hemorrhagic diathesis bronchopneumonia or sepsis death ensues within four weeks or less in 60 per cent of the patients and within eight weeks in 84 per cent.<sup>277</sup> None of 113 cases lived longer than twenty-six weeks.

The white cells which dominate the blood picture with usually over eighty per cent are uniform and immature mostly myeloblasts less often lymphoblasts or monoblasts. The blood platelets run low and the coagulation and bleeding times are prolonged. The absolute number of leukocytes may be about normal. Leukopenia is common in the early stages.

**Skin and Mucosal Manifestations.**—Forkner<sup>278</sup> emphasizes the importance of initial gingivitis as an aid in differentiation of the acute leukemias. It is most marked and diffuse in monocytic leukemia. Here it may extend to the pharynx usually causing ulceration and bleeding. More than in the other types a diffuse cellulitis is apt to appear about the lesions causing tooth ache and painful acute inflammation in the deeper tissues of the face. The patients are usually first seen by a dentist. If teeth are extracted the bleeding is severe and some times fatal. Deep necroses have followed such extractions. Several authors emphasize the submerging of the teeth in the swollen pale pink, soft and tender gums which bleed easily.<sup>279-282</sup> The oral aspect sometimes resembles scurvy. Besides the gingivitis gangrenous punched-out ulcerations in the floor of the mouth occur. The necrotic character of the leukemic infiltration may dominate the changes in the tonsils and the lymphoid tissues of Waldeyer's ring.<sup>283</sup> Noma resembling pictures may ensue.<sup>284,285</sup>

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<sup>277</sup>Warren & L. Acute Leukemia, Am J M Sc 378: 480-500, 1929.

<sup>278</sup>Pitts-Oberald, L. M. Oral Lesions in Leukemias, J Iowa M Soc 83: 424-426 1943.

<sup>279</sup>Pastermack, J. O. Abbott, O. A. and Werner, R. D. Leukemic Gingivitis by Case of Acute Aleukemic Leukemia, J Am Dent A 29: 1193-1197 1942.

<sup>280</sup>Osgood, E. E. Monocytic Leukemia. Report of 6 Cases and Review of 127 Cases, Arch. Int. Med. 109: 931-951 1937.

<sup>281</sup>Hertz, A. Klinische Beobacht. ugen bei der Lymphogranulomatose Wien Arch. f inn Med 261: 437-451 1934.

<sup>282</sup>Karl, W. Acute Myeloblasten-Leukämie, Zbl. 84: 72.

<sup>283</sup>Oeben, I. Cutaneous Tumors in Acute Myeloid Leukemia, Nederl tijdschr. geneesk pp. 1061-1033, 1930 Zbl. 84: 172.

<sup>284</sup>Epstein, T. Fall on akuter aleukämischer lymphatischer Leukämie mit ausgebreiteter spezifischer Hautveränderung, Fortschr. f. Bldg. Entz. pp. 43-49 1928 Zbl. 29: 652 1929.

<sup>285</sup>Guldberg, F. Zur Klinik der Leukämie entz. Venenot 7 23-37 1920 Zbl. 26: 206 1921.

<sup>286</sup>Kleinwiesner, O. Zur Kasuistik der Erythrämie mit Übergang in Leukämie, Klin. Wchnschr. 13: 985-990 1934.

especially in children<sup>3236,3237</sup>. Desquamation and dryness<sup>3466,3467</sup> without other characteristics of erythroderma, as well as petechiae are often noticed. Herpes zoster well known as a dermatome in other lymphoblastomas occurs in lymphogranulomatosis, too.<sup>3467,3468</sup>



Fig 315—Hodgkin disease. Nonspecific violently itching eruption. Note deep creases. Subsided after x-ray treatment of mediastinal and involved lymphatic nodes.

*Generalized exfoliative erythroderma* may be nonspecific or specific, or at first the former then the latter. It occurs in all degrees of severity. Its clinical

<sup>3236</sup>Freer W. Lymphogranulom bei Kindern. *Jahrb f Kinderh* 123: 145-166, 1920.

<sup>3237</sup>Schwarzhof, S. Die Lymphogranulomatose der Haut. *Handb d H. Gk* 8, 1: 271-323, 1929.

<sup>3466</sup>Paol F. Lymphogranulomatose mit eigentümlichen Verhornungsstörungen der Haut. *Dermatol Wochschr* 11: 1210-1211, 1929. *Zbl 23: 791*.

<sup>3467</sup>Roach P. Ichthyiform A rophy of Skin in Hodgkin's Disease. *Arch Derm & Syph* 47: 778-781, 1943.

<sup>3468</sup>Ponderas, E. and Fawcett, H. K. Herpes Zoster in Hodgkin's Disease. *Am J M Sc* 106: 326-333, 1922.



picture hardly differs from that in lymphoid leukemia<sup>237,240-241</sup> Ichthyosiform keratosis has been observed<sup>242</sup>

*Edema* is a feature in advanced Hodgkin's disease. It may involve a vast area or the whole body and be part of the cachexia. Of greater dermatological interest is the localized elephantastic edema of the penis and scrotum<sup>243</sup> and of the hands and feet<sup>244</sup>. Melanoderma may reach degrees which suggest Addison's disease. Such pigmentations have been observed in cases without preceding x ray or arsenic medication<sup>245</sup>. Hodgkin's disease has several times been seen to develop following unusually heavy pigmentation from sunlight exposure.<sup>7</sup>

*Specific Dermadromes—Tumors and Ulcerations*—This group includes papular rashes as well as infiltrations and larger lesions which one would be more inclined to call tumors. They are all of the same nature. There is no need to form a separate group of lymphogranulomatous ulcerations of the skin since no ulceration occurs without a preceding tumor.

Papular rashes consisting of more or less densely<sup>246</sup> placed cutaneous papules, resemble in their clinical appearance those encountered in leukemia. They may develop from preceding *prurigo lymphatica*.<sup>247</sup> A difference may perhaps be seen in the more pronounced regressive tendency of the lesions. Erosion ulceration and healing with scarification or central depression is common.<sup>248,249</sup> The lesions may be situated in varying depths of the cutis and subcutis thus varying in color and palpability. The rash mostly covers the trunk with a certain predilection for the sternal area. In some cases the lesions are grouped together in circinate<sup>250</sup> or corymbiform arrangement (Brunsguard after Schoenhof<sup>251</sup>). The number of such observations, however is too

<sup>237</sup>Schreiber. Lymphogranulomatose. Zbl. 88 307 1934.

<sup>238</sup>Lorvass. A. B. Cutaneous Manifestations of the Lymphoblastomas, Hodgkin's Disease. J. A. M. A. 104 1842-1848 1934.

<sup>239</sup>Wiley. J. E. M. Hodgkin's Disease With Erythroderma, Proc. Roy. Soc. Med. 24 81 1934.

<sup>240</sup>Bruck. C. Lymphogranuloma cutis maligna mit charakteristischer Histiozytendegeneration. Acta dermat. 20 397 1930.

<sup>241</sup>Lobe. La forme de Erythrodermie bei Hodgkin'scher Krankheit. Zbl. 82 563.

<sup>242</sup>Gougeon. H. Bism. P. Oberling and Kirschner. O. Atrophie de l'épiderme et de derme superficielle et déquotation interne généralisée de la peau (masse erythrodermique) dans à un lymphogranulomatose typique. Arch. dermat.-syph. Hôp. A. Louis 4 319-340, 1932.

<sup>243</sup>Tockmeyer. L. Erythema rubra di Hebra-Jadassohn in sogget. affetto da linfogranulomatose maligna di erenberg-Paltz. Giorn. Ital. di dermat. 37 1340-1344, 1930.

<sup>244</sup>Reprints. O. Di un caso di linfogranuloma Paltz-Sternberg (Eritroderma psitricus tipo Hebra). Paltz-Sternberg (see. word) 29 333-403 1930.

<sup>245</sup>Reprints. Lymphogranulomatose (Paltz-Sternberg) of Skin. Arch. f. Dermat. u. Syph. 181 720-760, 1941.

<sup>246</sup>Kirschner-Cervin. J. and de la Ossa. L. Elephantiasis of Penis and Scrotum in the Course of Malignant Lymphogranulomatose (Paltz-Sternberg). Acta dermo-sif. 29 734-738, 1930.

<sup>247</sup>Passey. O. Lymphogranulomatose. Zbl. 46 361 1933-1935.

<sup>248</sup>Kiehl. O. Jr. Pigmentierung bei Lymphogranulomatose (Paltz-Sternberg). Zbl. 84 6, 1937.

<sup>249</sup>Grubbs-Little. E. Lymphogranuloma cutis, Proc. Roy. Soc. Med. 24 1320, 1937.

<sup>250</sup>Swietner. E. K. and Wiser. L. H. Ulcerative Hodgkin's Disease. Arch. Dermat. & Syph. 51 329-330, 1918.

<sup>251</sup>Nohl. G. J. vesicle tubercles Lymphogranulomatose. Wien. klin. Wchnschr. 66 717-719 1933.

<sup>252</sup>Bruck. S. R. Cutaneous Hodgkin's Disease With Terminal Blood Stream Spread. J. A. M. A. 104 1035-1036 1934.

<sup>253</sup>Kiehl. Lymphogranulomatose cutis. Zbl. 88 307 1937.

<sup>254</sup>Dittrich. Lymphogranulomatose der Haut. Zbl. 41 606.

<sup>255</sup>Wash. Hodgkin's Disease. Arch. Dermat. & Syph. 33 125, 1930.



FIG 316



FIG 317



FIG. 318.

FIG 316 Papulo-nodular specific eruption in Hodgkin disease

FIG 317 - Papulo-nodular specific eruption in Hodgkin disease

FIG 318 - Hodgkin disease. Papulo-nodular specific eruption and transition in exfoliative erythroderma.

(From Berk R. J A. M. A.)

small to draw conclusions with regard to an infectious nature. The grouped lesions link with the cases with large tumors in small numbers. A large node or plaque may be surrounded by satellites.<sup>102,103</sup> Such plaques may reach hand size or may cover half of the scalp or even half of the chest<sup>101</sup> or one groin.<sup>101</sup> These giant plaques are quite suggestive of Hodgkin's disease and are rarely found in other lymphoblastomas. Tumors of the face<sup>102</sup> and of the ear lobes<sup>104</sup> sometimes in symmetrical arrangement<sup>105</sup> may create a facies leonina. Local trauma may be followed by development of tumors. The consistency of the tumors



Fig. 319. Hodgkin's disease. Ulcerated cutaneous tumor of the anterior chest wall.

varies with the depth and the degree of regression and scarring. An uneven firmness is a frequent finding (Wirz after Schoenhof<sup>106</sup>). The color of these lesions is described as red to dirty yellowish and brown. Most describers emphasize the tendency to ulceration and sinus formation.<sup>34</sup> The whole giant tumor plaque may become an ulcer with undermined<sup>107</sup> or infiltrated edges leading to invasion of deeper structures even bones.

<sup>102</sup>Greenberger, C. A. and Cornell, V. H. Lymphoblastoma (Hodgkin's Disease) of the Scalp. Case, Arch. Dermat. & Syph. 29: 560-572, 1921.

<sup>103</sup>Kierland, R. B. and Montgomery, H. Cutaneous Ulcerative Hodgkin's Disease. Proc. Staff Meet. Mayo Clin. 18: 124-125, 1911.

<sup>104</sup>Prinz, R. J. Hodgkin's Disease With Dermal and Subdermal Nodules and Purpura, Brit. J. Dermat. 42: 443-448, 1930.

<sup>105</sup>Kallion, R. H. Hodgkin's Disease of the Lymphatic System and of the Skin, Arch. Dermat. & Syph. 28: 1902-1903, 1937.

Sometimes underlying structures like lymphatic nodes are primarily involved, and the skin is invaded later in a scrofuloderma-like fashion.<sup>207-212</sup>

Specific oral lesions seem to be rare.<sup>211</sup> Paltau<sup>209</sup> suggested that the lymphatic tissues of Waldeyer's ring were the portal of infection but clinical oral or pharyngeal symptoms are very rare considering the frequency of cervical lymphomas. Only a few cases of ulcerative tonsillitis followed by specific neck nodes have become known.<sup>208,209</sup> The rarity of tonsillar lesions compared with the frequency of cervical lymph node involvement does not rule out the tonsils as portals of entry.<sup>209</sup>

Infiltrations and aphthoid lesions of the tongue as well as buccal pigmentations,<sup>208</sup> have been seen. In one case the tongue and oral mucosa and the glans penis showed a patchy exfoliation without any other skin manifestations.<sup>208</sup>

**Diagnosis and Histology**—The diagnosis of cutaneous lymphogranulomatosis rests mainly on the diagnosis of systemic Hodgkin's disease and on the histological findings in lymph nodes and in the skin lesions. The use of stained lymph node imprints on glass slides for the demonstration of characteristic cells has lately been recommended.<sup>208</sup> The specific lesions consist of foci of dense cellular infiltration in the corium and in the subcutaneous tissues. The infiltrate is made up of lymphoblasts small lymphocytes plasma cells, fibroblasts epithelioids mast-cells and granulocytes. Among the latter eosinophiles are sometimes found in large numbers. The most characteristic cell of the polymorphous granulation tissue is a large cell with much protoplasm and containing one or several deep-staining nuclei. These nuclei are usually large and rich in chromatin and contain nucleoli which stain deeply with eosin. Less often the nuclei are pale (Sternberg after Schoenhof<sup>209</sup>). These are the so-called Sternberg and Dorothy Reed giant cells. They are irregularly scattered throughout the granulation tissue which suggests a process of chronic inflammation rather than neoplasm. However transformation into true sarcoma occurs.

Tappeiner<sup>206</sup> emphasizes the almost constant occurrence of lipid filled phagocytes (pseudoxanthoma cells)

<sup>207</sup>Rick, W. Lymphogranulom, *Skd* 48: 14.

<sup>208</sup>Bureau, O. Drouot, P. L. Flervault, P. and Longot, P. Observation d'un cas de forme cutanée atrophique de la lymphogranulomatose scrofuleuse, *Bull. et mémo. Soc. Méd. d'hôp. de Paris* 49: 1144-1148, 1933.

<sup>209</sup>Paltau, F. E. and Caro, M. R. Ulcerative Hodgkin's Disease of the Skin, *Arch. Dermat. & Syph.* 35: 14-24, 1937.

<sup>210</sup>Paltau, F. E. Über die Übertragbarkeit des Virus der Lymphogranulomatose, *Wien. klin. Wochenschr.* 42: 437-439, 1930.

<sup>211</sup>Virehes, J. Madaia, G. and Roussel, J. Un cas d'adénite tonsillitique primitive (maladie de Paltau-Sternberg), *Bull. Soc. franç. de dermat. et syph.* 48: 369-372, 1932.

<sup>212</sup>Zellin, S. Eine seltene Nachschübländerung bei Lymphogranulomatose, *Monatsschr. f. Ohrenh.* 63: 778-783, 1929.

<sup>213</sup>Richter, F. Lymphogranulomatose mit Mastzelleninfiltraten, *Arch. f. Dermat. & Syph.* 135: 31-39, 1931.

<sup>214</sup>Karl, H. Hodgkin's Disease: Surface Lymphogranulomatosis Confined to the Oral and Perioral Areas, *Curr. Arch. Dermat. & Syph.* 24: 244-250, 1931.

small to draw conclusions with regard to an infectious nature. The grouped lesions link with the cases with large tumors in small numbers. A large node or plaque may be surrounded by satellites.<sup>212,213</sup> Such plaques may reach hand size or may cover half of the scalp or even half of the chest<sup>214</sup> or one groin.<sup>211</sup> These giant plaques are quite suggestive of Hodgkin's disease and are rarely found in other lymphoblastomas. Tumors of the face<sup>215</sup> and of the ear lobes<sup>216</sup> sometimes in symmetrical arrangement<sup>217</sup> may create a facies leonina. Local trauma may be followed by development of tumors. The consistency of the tumors



FIG. 319.—Hodgkin disease. Ulcerated cutaneous mass of the anterior chest wall.

varies with the depth and the degree of regression and scarring. An uneven firmness is a frequent finding (Wirz after Schoenhof<sup>218</sup>). The color of these lesions is described as red to dirty yellowish and brown. Most describers emphasize the tendency to ulceration and sinus formation.<sup>219</sup> The whole giant tumor plaque may become an ulcer with undermined<sup>220</sup> or infiltrated edges leading to invasion of deeper structures even bones.

<sup>212</sup>Greenbester, C. A. and Cornell, V. H. Lymphoblastoma (Hodgkin's Disease) of the Scalp. *Cases, Arch. Dermat. & Syph.* 29: 509-573, 1924.

<sup>213</sup>Kierland, R. R. and Montgomery, H. Cutaneous Ulcerative Hodgkin Disease. *Proc. Staff Meet. Mayo Clin.* 16: 124-128, 1911.

<sup>214</sup>Drain, R. J. Hodgkin's Disease With Dermal and Subdermal Nodules and Purpura. *Brit. J. Dermat.* 43: 443-448, 1920.

<sup>215</sup>Radcliff, R. H. Hodgkin Disease of the Lymphatic System and of the Skin. *Arch. Dermat. & Syph.* 24: 1202-1203, 1927.

nodules in the skin or in the subcutaneous tissue. Their number may be very great.<sup>329,348-511</sup> There is a definite tendency to spontaneous regression which is rarely found in metastases of other malignant tumors. The metastatic nodules are occasionally seen in close proximity to the primarily involved lymph node.<sup>329</sup>

Sometimes mediastinal lymphosarcoma penetrates the chest wall and invades the skin. Even such advanced lymphosarcoma may still be clinically curbed by x ray therapy. The incidence of metastatic nodules in the skin is given as 5 per cent<sup>329</sup> and as 13.9 per cent of 122 cases.<sup>340</sup>

The diagnosis is usually assured by biopsy. There is profuse proliferation of a single type of cell invasion of the capsule of the node and the neighboring tissues, abundance of atypical lymphoid cells without notable endothelial and reticulum hyperplasia and lack of Sternberg Reed cells.<sup>342</sup> Differentiation from other lymphoblastomas is not always possible.<sup>3419</sup> The therapy is radiological and surgical.

<sup>329</sup>Kitch, G. Jr. Ekterschneidungen bei akuten Lymphosarkomaten übergrößerer Lymphknoten. *Arch. f. Dermat. u. Syph.* 1894: 300-311 1895.

<sup>340</sup>Kiebs. Fall zur Diagnose. *Ebl.* 65: 11.

<sup>341</sup>Plano. Lymphosarkomatöse Cutis. *Ebl.* 39: 618.

<sup>342</sup>Cohn, R., and Richter M. Modern Views on Hodgkin's Disease. *M. Rec.* 148: 343 1925.

## CHAPTER XXXIII

# DISORDERS OF THE BLOOD AND THE BLOOD FORMING ORGANS

### Anemias<sup>7982, 7984</sup>

The red blood cells are formed in the endosthelium in the red bone marrow. They pass through various stages of development (megakaryoblast, normoblast, reticulocyte) before they are released into the blood stream. Besides the material necessary for the development of all cells, two specific substances are required for the normal development of erythrocytes: iron for the formation of hemoglobin and the erythrocyte maturing factor (EMF) which is produced in the gastric mucosa and stored mainly in the liver. After a life span of from two to six weeks, the red cells die and their remnants are phagocytized by the reticulo-endothelial cells in the spleen. Eighty-five per cent of the iron is used again and bilirubin, the other end product, is under normal conditions excreted by the liver.

The function of the red cells is the transport of oxygen from the lungs to the tissues. Anemia is a reduction below normal of the capacity of the blood to transport oxygen.<sup>7980</sup> It may result from too small numbers of functioning red cells or from deficiency in their function, due especially to lack of hemoglobin. The clinical forms and stages of anemia are mostly explained by the phase in which a damaging influence hits the growing or mature red cell. For example, in the case of anemia from massive hemorrhage the mature cells are reduced in number. In the case of pernicious anemia the maturing of the red cells within the bone marrow is disturbed by a deficiency of the EMF and so they die to a large extent in the bone marrow, only an insufficient number of immature cells being released. The bilirubin left over from the hemoglobin of the masses of dead red cells increases the bile pigment in the blood and may cause icterus.

**Dermadromes.**—*Pallor* is seen in practically all anemias and is directly proportional to the loss of hemoglobin.<sup>7981</sup>

In *hypochromic anemia* (chlorosis) which is rare today, the pallor sometimes takes on a slightly greenish tinge. Capillaroscopy shows the capillaries in various types of severe anemia to be pale, thin, or even empty and filament like with the arterial and venous sections hardly discernible.

The estimation of pallor from the face and the mucosae is often deceiving. Duke advises a quick test: compare the palms of the patient with those of a normal person. The palms should be held at heart level. The advantage of the test which supposedly is quite accurate, is the independence of the palms to emotional erythema and light.

<sup>7982</sup>Mettenberger, E. Some Etiological Factors in Pernicious Anemia. A Symposium on the Blood and Blood Forming Organs, Madison, Wis. 1930 the University of Wisconsin Press.

Chevallier<sup>342</sup> enumerates the following dermatoses as occasionally seen in essential anemias: Rhagades of the fingertips and lips, smooth atrophic tongue and buccal mucosa, pruritus vulvae, precocious graying of the hair and intertriginous erythema. Corroboration of these impressions is still lacking although a similar list which includes collonychia is given by Simon.<sup>343</sup>

### Pernicious Anemia

Besides the pallor found in other anemias too a yellowish discoloration is characteristic of this disease. It is caused by the increased content of bilirubin from prematurely destroyed red cells and to a lesser extent from other substances in the blood plasma. The icteric index may be above ten normal is four to six. The third factor which influences the color in pernicious anemia is pigmentation which though rarely may reach degrees which suggest Addison's disease. The pigmentation is mostly described as diffuse sometimes it has a predilection for the trunk, chest, abdomen and the dorsa of the hands. As in Addison's disease the creases, folds or scars may be darker than the surrounding skin.<sup>344</sup> Freckled or lentigo-like spots have been seen within the diffuse melanoderma (Lennartz after Kaufmann<sup>156</sup>). Another similarity to Addison's disease is found in slate-colored or brownish spots on the oral mucosa. Not only may the symptoms of Addison's disease occur in pernicious anemia but even post mortem findings of adrenal atrophy are on record.<sup>157</sup> Bogorad<sup>345</sup> saw improvement of the pigmentation under cortin while liver therapy alone failed to change it. Most authors suggest that the melanosis in pernicious anemia is a hemosiderosis derived from the blood but the histological evidence is scanty and not clear.<sup>346-348</sup> The possibility of arsenical melanosis must be considered since arsenic was and still is used in pernicious anemia. Patients with pernicious anemia under treatment with liver extract are supposed to tan more readily than normal persons.<sup>349</sup> In a very extensive case of cutaneous and mucosal pigmentation in pernicious anemia the author could not notice any effect of liver therapy on the pigmentation despite good response of all other symptoms. Ulcers of the lower legs which are more often seen in other forms of severe anemia are very rare in pernicious anemia.<sup>347</sup>

The symptom known as *Möller's or Hunter's glossitis* is of practical importance because it may precede all other complaints and the hematological findings

<sup>342</sup>Chevallier, P. *Die Dermatosen der Anemien*, Med. Welt 10: 120-122, 1930.

<sup>343</sup>Simon, C. *Anémie*, etc., Paris 4<sup>ed.</sup> 1: 47-51, 1930.

<sup>344</sup>Bogorad, A. B. Hyperpigmentation of skin in Biermer's Anemia, Klin. med. 19: 94-95, 1940. *Id.* 23: 104.

<sup>345</sup>Kocucha, J. B. and Paxton, P. M. Case of Erythrodermia With Lymphocytosis, Brit. J. Dermat. 53: 373, 1921.

<sup>346</sup>Ganssberg, E. Hautpigmentation und Hautreaktion bei perniziöser Anämie, Deutsche med. Wochschr. 57: 1374, 1931.

<sup>347</sup>Michaux, T. Pigmentierungen der Haut bei perniziöser Anämie, Arch. f. Dermat. u. Syph. 131: 746-751, 1919.

<sup>348</sup>Laach, F. Blutgeschwüre bei perniziöser Anämie, Deutsche med. Wochschr. 53: 377-378, 1928.



## PLATE V

- 1 Pellagra. Erythema of dorsum manus. (Courtesy Wisconsin General Hospital)
- 2 Scurvy. Gingivitis. (Courtesy Wisconsin General Hospital)
- 3 Ecchymoses of acute lymphatic leukemia. (Patient of Dr. F. Kay)
- 4 Pernicious anemia, untreated. Acute glossitis involving mainly the edges. Filiform papillae are still present. Not ecchymoses.
- 5 Pernicious anemia. Pale slick tongue. Atrophy of papillae.
- 6 Erythema nodosum.



PLATE V



in pernicious anemia.<sup>302-306</sup> The condition starts with a burning sensation in the tongue and occasionally in other parts of the mouth. The pain and sensitivity to acid, hard food and smoking often comes in spells. Sometimes articulation is hampered. In some cases only burning is noticed and no visible changes develop but more often fiery red, painful round or oblong erosions appear usually on the dorsum close to the tip. The filiform papillae within the patches are at first swollen but soon thinned or absent; the fungiform papillae are often swollen and red.<sup>303,304</sup> The tip and the edges occasionally also the adjacent parts of the dorsum of the tongue are involved but sometimes also the inside of the lips,



FIG. 220.—A. Pernicious anemia. Subchronic changes. The papillae filiformes have mostly disappeared. B. Pernicious anemia. Atrophy of papillae.

cheeks and the palate (Harris after O. H. Foerster<sup>306</sup>). From the distribution on the tongue a "V" or "U" shaped figure results with the opening directed toward the base of the tongue. Many authors<sup>307</sup> emphasize the contrast of the fiery red lesions on the tongue to the pallor of the other parts of the oral mucosa while others say that the red areas are the healthy ones and the pale areas the changed ones.<sup>303</sup> These may represent later stages of development. The initial erosion is later followed by atrophy of the papillae which results in a smooth surface. In extreme cases the atrophy may involve the posterior part of the tongue and the

<sup>302</sup>Maget, W. Zur Kenntnis der Glossitis bei perniziöser A. *Klin. Wochenschr.* 1932, 9: 318-31. 1932.

<sup>303</sup>Heym, W. Möller'sche Glossitis, Hunter'sche Zunge und perniziöse Anämie. *Dermat. Ztschr.* 47: 122, 1934.

<sup>304</sup>Flaschke, A. Möller'sche Glossitis. *Die Haut.* 1933, 2: 89-782.

<sup>305</sup>Hunter, W. *Severe Anemias: Their Infective Nature, Diagnosis and Treatment*, London, 1909.

<sup>306</sup>Foerster, O. H. *Dermat. eru. and Associated Diseases of the Mucosa*. J. A. M. A. 73: 853, 1919.

<sup>307</sup>Zimmer, E. Hautkrankheiten und Mundkrankheiten. Möller'sche (Hunter'sche) Glossitis. *Handb. d. H.* 16, 1: 11, 1930.

papillae vallatae. Slight edema of the tongue with visible impressions of the teeth has often been noticed in the early stages (Hunter's<sup>344</sup> 'hacked edges').

Though most frequently seen in pernicious anemia Möller-Hunter's glossitis or similar conditions occur in other severe anemias (tropical and nontropical sprue, pellagra, alcoholism, tapeworm, etc.)<sup>345</sup> The painful red erosions of Möller-Hunter's glossitis should not be confused with the dry, round, sharply outlined plaques *fauchées* which are seen in syphilis or with the harmless plaques *lisses* which consist of non-inflammatory round areas which are devoid of papillae. These completely painless lesions are usually accidental findings. The transitory character and the fast traveling over the dorsum within a few days are characteristic of the wandering rash of the tongue. The restriction of a chronic inflammation to a diamond-shaped area in the center of the posterior tongue marks the rhombic median glossitis.<sup>346</sup> Liver therapy relieves the glossitis in pernicious anemia and so it has become rather rare. If the patient sticks his tongue out, anemic stripes appear which correspond to the contracted muscles (Arndt after Heyn<sup>347</sup>). This sign is considered valuable in early diagnosis. The tongue is hardly ever coated.

### Sickle Cell Anemia

This is a severe hereditary anemia which derives its name from the characteristic sickle- or spindle-shaped erythrocytes (drepanocytes) which occur in great numbers, as do other bizarre forms of the red cells. The disease has almost exclusively been seen in Negroes, in a few instances in Sicilians.<sup>348</sup> Jaundice is almost always noticeable.<sup>347</sup>

**Dermadromes.**—Punched out, sometimes serpiginous, unilateral or bilateral, extremely chronic ulcers near the ankles are common in this anemia. They were seen in twenty out of twenty-eight cases<sup>349</sup> and in 55 out of 214 cases.<sup>350</sup> These ulcers often develop after minor injuries. Poor circulation in the lower legs and the known tendency to thrombosis in sickle cell anemia probably are pathogenetic factors. Priapism, which has repeatedly been seen in sickle cell anemia, also can be explained by thrombosis in the vascular system of the penis.<sup>349</sup>

Therapy of the ulcers should consist of nonirritating local medication and treatment of the underlying anemia.

Similar leg ulcers have been seen in a considerable number of cases of *hemolytic anemia* (hemolytic jaundice). This is a hereditary anemia characterized by unusual spheroid shape of the erythrocytes. These ulcers sometimes only heal

<sup>344</sup>Alanson Bahr, P. H.: Glossitis and Vitamin B Complex I: Pellagra, Sprue and Allied States. *Lancet* 21: 517-550, 1940.

<sup>345</sup>Brocq and Pastrick: *Journal desantique médiane ans de dermat et syph* 5: 1, 1914-1915.

<sup>346</sup>Greenwald, E. and Burrell, J. B.: Sickle-cell Anemia in White. *Pediatrics* 11: 789-794, 1940.

<sup>347</sup>McGavack, T. B. and Nussbaum, C. C.: Skin Manifestations of Sickle Cell Anemia. *Urol. & Gynec. Rev.* 44: 194-200, 1949.

<sup>348</sup>Cosman, C. L. and LaRocca, C. G.: Ulcers of Legs in Sickle Cell Anemia. *Arch. Dermat. & Syph.* 42: 1015-1029, 1940.

<sup>349</sup>Gettoff, P. L.: Priapism and Sickle Cell Anemia. *J. Cases J. Urol.* 48: 97-111, 1942.

after splenectomy<sup>107b-114</sup> The jaundice in hemolytic anemia supposedly does not itch as other types of icterus usually do<sup>115</sup>



Fig 321 - Female aged 18 years Sickle cell anemia Leg ulcer (From McGuck, T. H. *Urol. & Cutan. Rev.* 1942)

<sup>107a</sup>Taylor E. S. Chronic Ulcer of the Leg Associated With Congenital Hemolytic Jaundice. *J. A. M. A.* 172:1574-1938

<sup>107b</sup>Ensaye F. de A. Ulcus cruris y esplenectomia en ictericia hemolitica. *Rev. de cir. Barcelona* 11: 17-139, 1911

<sup>107c</sup>Lanzl F. J. Unterschenkelgeschwür bei hämolytischem Ikterus. *Klin. Wchnschr.* 18: 400-410, 1931

<sup>107d</sup>Kippinger H. Schwer heilbare Pustelgeschwüre bei hämolytischem Ikterus. *Klin. Wchnschr.* 8: 16-12, 1930

<sup>107e</sup>Pepper E. Ein Fall von Ikterus hemolyticus mit Unterschenkelgeschwür. *Mitt. Gesellsch. Verh. med. f. Langenbruck* 66: 703-710, 1924 *Klin. Wchnschr.* 223.

**Hypochromic Anemia Plummer Vinson Syndrome**—Dysphagia, an atrophic oral mucosa anemia and often spoon nails or thin nails constitute a syndrome which does not seem to be rare. Described by Vinson<sup>217</sup> in 1922 as hysterical dysphagia but observed before it has been confirmed by reports from many countries. It seems to occur more frequently in Sweden than in other countries.<sup>218</sup> The patients are almost exclusively women mostly in middle age. Idiopathic hypochromic anemia with pallor but without jaundice is the most



Fig 323.—Female aged 16 years. Severe sickle cell anemia. Hemoglobin 40 per cent. R. B. C. 166 million. Hemolytic icterus. Amenorrhea. Ulcer of the lower leg exists for 4 years without any response to treatment. It developed after dog bite. (From McO'rack, T. H. *Urol. & Cutan. Rev.* 1943.)

constant feature of the syndrome.<sup>217</sup> The red cells usually do not fall below 4 000 000 but the hemoglobin is reduced to 50 per cent or less. Achlorhydria is seen in 75 to 90 per cent of the cases and moderate splenomegaly in

<sup>217</sup>Vinson, P. P. Hysterical Dysphagia, *Minnesota Med.* 8: 107 1922.

<sup>218</sup>Ahlborn, H. B. Achlorhydric Anemia, Plummer Vinson Syndrome and Carcinoma of the Mouth, Pharynx, Esophagus in *W. med. Brit. M. J.* 2: 331-333 1936.

<sup>219</sup>Anderson, N. P. Spoon Nails, Anemia, Onychitis and Dysphagia, *Arch. Dermat. & Syph.* 37: 816-823, 1936.

25 per cent. Complaints of burning tongue especially after eating fruit and other acid food often lead the attention to the changes in the mucosa of the upper part of the gastrointestinal tract. The patients have great difficulty in swallowing solid food so that their mealtime is prolonged.

They soon arrive at a liquid or semiliquid often deficient diet.

**Dermadromes and Oral Manifestations.**—There is cheilitis varying from minor fissures to hypertrophic chronic inflammation or perlèche. Buccal leukoplakia occurs. After a time the lips become thin and the mouth shrinks. Ahlborn<sup>3476</sup> who has given a very detailed description believes that the shrinking of the lips is part of the same atrophic process which leads to the changes in the tongue and esophagus. Possibly the fact that these patients often lose their teeth early has some significance. The surface of the tongue is described as glazed red dry smooth and devoid of papillae.<sup>3477,3478</sup>

There is much similarity to Hunter's glossitis but the involvement of the mucosa seems more widespread and more constant. It not only involves the mouth but it extends to the upper—rarely the lower<sup>3482</sup>—part of the esophagus. Spastic or cicatricial stenosis of the mouth of the esophagus web formation across the lumen ulceration and other symptoms have been seen.<sup>3478,3479</sup> Cancer of the esophagus and multiple oral malignancies have been observed. Especially in the relatively rare instances of cancer of the lip in women should the thought of anemia and Plummer Vinson's syndrome enter the mind.<sup>3478,3479,3479</sup> The post-cricoid cancer of the esophagus which in 70 per cent to 90 per cent is encountered in women probably belongs here.<sup>3479</sup> Association of Plummer Vinson syndrome and kraurosis vulvae is also known (Rhoads after P. Gross<sup>3487</sup>).

Only recently after many cases of Plummer Vinson's syndrome have been described without mentioning koilonychia has a spoon nail been discovered to form a rather frequent (about 70 per cent) dermatome in hypochromic anemia.<sup>3488</sup> <sup>3478,3477</sup> The free edge of the nail is thin and sharp as if gnawed on. The nail breaks or splits easily and in less complete cases the nail is only flat and thin. It should not be forgotten that koilonychia may be produced by occupational factors, e.g. work in soap suds and oils. Dry gray pepper and salt hair are also mentioned in case reports.<sup>3489</sup> The similarity of Plummer Vinson's syndrome with ariboflavinosis has been emphasized.<sup>3488</sup>

The treatment of the syndrome consists of administration of iron in liquid form hydrochloric acid riboflavin<sup>3488</sup> and bougiening of the upper esophagus which seems to be particularly helpful in relieving the dysphagia and facilitating a proper diet. The oral as well as the nail changes are capable of complete restoration.

<sup>3476</sup>Kernan, J. D.: Plummer Vinson Syndrome 3 Cases. Arch. Otolaryng. 52: 663-677 1940.

<sup>3477</sup>Gertman, P. O.: Disorders of Mouth of Esophagus in Syndrome of Plummer Vinson (Dysphagia With Anemia). J. Laryng. & Otol. 55: 143-153, 1940.

<sup>3478</sup>Dameshek, W.: Primary Hypochromic Anemia. J.A.M.A. 80: 548, 1923.

<sup>3479</sup>Neubergsch, E. and Dickel, J.: Riboflavin Avitaminosis and Plummer Vinson Syndrome. Klin. Wochenschr. 20: 431-432 1941.



## Granulopenia (Agranulocytosis)

Granulopenia<sup>207,217,218</sup> is a deficiency of the blood in granulocytes caused by failure of the bone marrow to produce or release these cells. It may be caused by toxic and allergic reactions<sup>219</sup> to drugs such as arsphenamine triiodophenol benzol amidopyrine sulfonamides and gold by radiant energy by infection and by allergic reaction<sup>219</sup>. Granulopenia also occurs secondarily to hyperplastic processes in pernicious anemia or leukemia. Low leukocyte count—sometimes as low as fifty—acute sore throat exhaustion severe malaise fever and a moderate degree of icterus are in 50 per cent of the cases the manifestations of this dangerous disease. The spleen is often enlarged. Cases without any mucosal symptoms occur<sup>220</sup>. The red cell and platelet counts are essentially unaltered this accounts for the usual lack of hemorrhagic symptoms.<sup>217,218,219</sup> If they too are deficient (pan myelophthisis) hemorrhages occur.<sup>21</sup> The resistance to infections is extremely low. The mortality in untreated cases was seventy-eight per cent in a large series.<sup>21</sup> Death may occur within thirty-six hours from the apparent onset.<sup>218</sup>



Fig 323—Agranulocytosis Ecthyma

- <sup>207</sup>Haxter R J. Agranulocytic Angina, M. Clin. North America III 1609-1641 1923.  
<sup>208</sup>Martin A. La granulopénie maligne. L'Union méd. d. Canada 66 196, 250, 349, 400 1940.  
<sup>209</sup>Madison F W and Squier T L. Agranulocytosis, J.A.M.A. 1923; 785-790 1924.  
<sup>210</sup>Clemens G. Granulocytopenia in Lepus Erythematosis, Dermat. Wechnchr 188 1210-1212 1930.  
<sup>211</sup>Jackson H J and Tighe T J G. Treatment and Mortality of 300 Cases of Acute Agranulocytic Angina, New England J Med 229: 729-732 1930.  
<sup>212</sup>Pham P. Clinical and Experimental Investigations in Agranulocytosis, London 1937 H. K. Lewis Co. Ltd and Copenhagen, 1937 Nyt Nordisk Forlag Arnold Busck.  
<sup>213</sup>Blaschke R. Agranulocytosis and Panmyelophthisis. München med. Wechnchr 66 1419-1423 1923.

**Oral Manifestation and Dermadromes.**—Angina is so much a part of the syndrome that the disease is often referred to as agranulocytic angina. Bucco-pharyngeal lesions are seen in 84 per cent.<sup>102</sup> The soft palate, uvula and anterior



Fig. 224.—Agranulocytosis. Ecchymoses. (Courtesy Dr. Erich C. Beck.)



Fig. 225.—Agranulocytosis. Cheilitis and glossitis. Patient also had nasitis.

pillars are red and eroded, the redness being sharply bordered against the normal mucosa.<sup>103</sup> The tonsils are enlarged and red, sometimes with small white specks, sometimes with severe ulcerations. Ulcerations in other part of the oral cavity and also in the nose<sup>104</sup> have been observed, sometimes without involvement of

<sup>102</sup> H. Retzl, A. C. (author's) *apud* With Fretille Changes in Nasal Mucosa, Monographs of Otolaryngology, 75, 636-637, 940.

the tonsils.<sup>2110</sup> Gingivitis with adherent foul smelling pseudomembranes<sup>2111,2112</sup> is often present. The gums bleed easily. Rarely the ulcerations invade the bone or spread to the deeper tissues of the pharynx and larynx. Edema of the glottis may necessitate tracheotomy.<sup>2113,2114,2115</sup> Fusiform bacilli and large spirilla are commonly found. The cervical lymph nodes are swollen but there is no generalized adenopathy.



Fig. 235. Agranulocytosis due to diathrophenol poisoning. (Courtesy Dr. Arthur F. Eckert.)

The face is often cyanotic, sometimes pallid or congested.<sup>2117</sup>

Cutaneous ulcerations about the body openings, mainly around the mouth and nose, were described by Landsberg.<sup>2118</sup> These necrotic lesions are mostly small<sup>2119</sup> but severe edema and lymphangitis may be present so that anthrax or other infections are simulated. Cellulitis and deep noma-like destructions are rare events. Ulcerations in the neighborhood of the anus<sup>2120</sup> or the genitalia<sup>2121</sup> have been observed quite frequently.<sup>2122,2123,2124</sup> Exanthems of erythematous pemphigoid, vesicular, papular or hemorrhagic<sup>2125</sup> character and occasionally

<sup>2110</sup> Ballard, M. and Leborg, L. Syndrome agranulocytaire à début buccal. (Général de la nécrose buccale. Fréquence des syndromes subcutanés avec anomalies périkératose. Rev. de m. natol. 28: 621-627, 1933. Ebl. 47: 584.

<sup>2111</sup> Dahmer, Agranulocytose. Ebl. 48: 234.

<sup>2112</sup> Krause, Dtsch. Dtsch. Ebl. 41: 289.

<sup>2113</sup> Potheven, W. J. Bilaterale Larynxschwellung bei Agranulocytose. Arch. f. Otolaryng. 147: 106, 1939-1940.

<sup>2114</sup> Heinsworth, J. J. and Meulders, M. Agranulocytosis With Buccopharyngeal Manifestations. 2 Cases. Ann. oto-laryng. pp. 231-237, 1940.

<sup>2115</sup> Landsberg, M. Hautveränderungen bei Agranulocytose. Med. Klin. 28: 1292-1293, 1930.

<sup>2116</sup> Beck, R. W. Agranulocytosis With Anal Ulcer. J. A. M. A. 83: 1468-1469, 1929.

<sup>2117</sup> Reye, E. Leber Haut- und Schleimhautveränderungen bei der Agranulocytose. Dermat. Wchnsch. 59: 1895-1899, 1933.

<sup>2118</sup> Fortier, L. Agranulocytose nécrose cutanée. Union méd. d. Canada 61: 246-250, 1934.

<sup>2119</sup> Graessmann, S. S. Acute Cutaneous Infection Associated With Agranulocytosis or Agranulosis. Arch. Dermat. & Syph. 28: 125-130, 1933.

<sup>2120</sup> Deloss and Fabre, J. Les lésions cutanées de l'agranulocytose. Arch. d. mal. d. coeur 27: 645-654, 1934.

<sup>2121</sup> Allen, W. Agranulocytic Angina With Thrombopenic Purpura. Ann. Int. Med. 2: 513-544, 1933.

typical erythema exudativum multiforme have been recorded <sup>3482,3487,3540,3573,3588</sup> Marin<sup>348</sup> has seen giant herpes of the lips. Pentnucleotide in large doses a stimulant for the production of leukocytes is considered helpful by many authors. Otherwise, the therapy is symptomatic. Recently pyridoxin by intravenous injection has been recommended <sup>3481</sup>

### Polycythemia<sup>3482</sup>

Compensatory increase of the erythrocytes (above 6 000 000 in men and above 5,500 000 in women) occurs under various suboxemic conditions e.g. low barometric pressures carbon monoxide poisoning and certain types of heart disease. Such secondary increases of the red cells hardly ever exceed 8 000 000. Polycythemia vera is a disease of the bone marrow. In this condition much higher sometimes enormous increases of the blood volume and of the red cells per cubic millimeter of blood occur. The viscosity of the highly corpuscular blood, of course is high. After an asymptomatic phase which may last years cyanosis, dizziness, headache and quite often hepato-splenomegaly develop. Bleeding occurs from the nose and gums due to congestion rather than to a hemorrhagic tendency. Variations of the normal syndrome include combinations of hypertension and especially in the final stages leukemia and anemia. <sup>3483</sup>

Dermadromes.—The most common and at the same time most striking dermadrome of marked polycythemia is the redness of the skin. This discoloration is most marked on the hands and face although in some cases it may be noticed over the entire body surface. The shade and intensity of the erythema varies from a dusky purple cyanosis to a deep orange in spots bright red. Red as a rose in summer and blue as indigo in winter is descriptive of the changes under the influence of weather and temperature. Osler<sup>3484</sup> who used this description said that one of his patients was jokingly called the "blue baby." There is erythema in areas which usually do not take part in other erythemas, e.g. the temples and the skin under the ears and between eye and nose. The redness of the conjunctivae creates an impression of rage. Contrary to congestion from other causes the redness stays constant during rest and sleep. <sup>3485</sup> While the erythema seems to be fairly even one can on close inspection and under glass pressure detect telangiectases on the red background. This is particularly true of the mouth. Capillaroscopy shows that the capillaries are dilated. It is here and in the spleen where much of the excess blood is bottled up <sup>3483</sup> Superficial telangiectases on the face often give the patient a ruddy complexion. Besides

<sup>3482</sup>Gorter: Agranulocytosis Vedet Udgave, Copenhagen p. 372 1939. Ekl 62: 58

<sup>3483</sup>Ellman, P. and La. royer J.: Agranulocytosis With Purpura Hemorrhagica Following Gold Therapy Prevention of Cerebral Ischem. Brit. M. J. 3 632-633 1933

<sup>3484</sup>Kawthorn: Treatment of Leukopenia and Granulocytopenia With Pyridoxine. Acta Med. Scand. 135 326, 1946

<sup>3485</sup>Kasnerthal, N. and Nauser, F. A.: Polycythemia. Course Arch. Int. Med. 62: 903-917 1933

<sup>3486</sup>Osler, W.: Chronic Cy. anemia. With Polycythemia and Enlarged Spleen. New Clinical Pathology 4 34-37 1929

<sup>3487</sup>Dewitke, O. and Dorchner, E.: Polycythemia. Med. Klin. 36 1654-1655, 1930

<sup>3488</sup>Brenna, C. E. and Aboud, C. H.: Measurements on the Skin Capillaries: Cause of Polycythemia Vera. Role of the Capillaries in the Production of Erythrocytes. J. Clin. Investigation 2 423, 1926.

linear telangiectases small deep cherry red papular hemangiomas are known to occur in polycythemia

The color of the oral mucosa is deep cherry red. Relatively early in the course of the disease the soft palate may appear considerably redder than the hard palate so that the borderline is marked.<sup>249</sup> In the cyanotic stage the tongue is swollen deep purple and the papillae atrophic. Bleeding from the blood gorged gums occurs but is slight since there is no hemorrhagic tendency.<sup>249,251</sup>

Small pigmented spots are often scattered over the reddened areas. They are probably due to hemosiderin deposits after small hemorrhages.

Telangiectases and petechiae constitute the elements of *purpura annularis telangiectodes* a dermatosis which has been found to be a dermatome of a considerable number of milder cases of polycythemia.<sup>249,254</sup> Without preceding hyperemia or infiltration small lavender to purplish colored spots appear. These maculae consist of capillarectases and petechiae. The lesions appear in crops. They often start in a follicle and spread peripherally leaving a slightly atrophic scar and resulting in rings<sup>251</sup> and polycyclic figures.

The tourniquet test is usually negative

The viscosity of the blood the high platelet content the large blood volume and the high blood pressure favor a variety of vascular disturbances

Thrombosis has been observed in many organs and is together with arteritis responsible for gangrene ranging in severity from the blistering of a toe to the loss of an extremity.<sup>255</sup> Various alterations of the lower legs have been observed.<sup>244-251</sup> Circulatory disturbances account also for the many instances of paresthesias Raynaud-like symptoms and transitory painful red warm areas similar to erythromelalgia.<sup>251, 256</sup> Norman and Allen<sup>257</sup> reporting on ninety eight cases of polycythemia mention arterial disease in 33 per cent.

Rosacea in polycythemia has been described several times, although some of the cases had better be grouped with *acne urticata* a relatively rare dermatome of polycythemia. *Acne urticata* is a chronic itching dermatosis which resembles prurigo quite closely. It starts in the face but has a tendency to involve the back and the extensor surfaces. It develops from an urticarial papule with a

<sup>249</sup>Kupferman D J Symptomatology of Erythremia, Vest. Otol. L. d. 34 210-213, 1937. Ebl. 27 406

<sup>250</sup>Wachtel O Skin Changes and Pathogenesis of Vagous Disease. Venerologia i dermatologia, pp 744-765 1926. Ebl. 23 673

<sup>251</sup>Wachtel O Skin Changes i Erythremia, Ebl. 20 37 1926

<sup>252</sup>Quarles H Purpura Majocchi, Arch. f. Derm. Syph. 189: 325, 1929

<sup>253</sup>Winkler F Purpura annularis telangiectodes Majocchi. Ebl. 30 547 1931

<sup>254</sup>Winkler H Die Veränderungen bei Polycythemia rubra, Dtsch. Dermat. 1937

<sup>255</sup>Hecker F Extremitätennekrose bei Polycythemia vera, Klin. W. kocher 11 1290-1293, 1933

<sup>256</sup>Thiele Trophoneurotisches Ulcus, Ebl. 25: 786

<sup>257</sup>Zetter W J Peripheral Vascular Disturbances i Polycythemia, M. Clin. North America 24 455-492 1940

<sup>258</sup>Hallam Ulcerated Nodules on Legs Associated With Splenomegalic Polycythemia, Brit. J. Derm. 43: 283-283 1930

<sup>259</sup>Graf F Ein Fall einer hochgradigen Erkrankung von Erythromelalgie und Polycythämie. Monat. Klin. 11 24-33, 1930. Ebl. 33 63.

<sup>260</sup>Glass O Polycythemia Vera, Virchow Arch. f. path. Anat. 263 345-373 1937. Ebl. 34 62.

<sup>261</sup>Norman, I. L. and Allen, E. V. Vascular Complications of Polycythemia, Am. Heart J. 12 367-374 1937

central vesicle which soon becomes excoriated. The crust covered lesion may ulcerate and heal with a pigmented scar. Crops of new lesions follow each other. The condition has much similarity to prurigo lymphatica, which occurs in leukemia. Thus *acne urticata* represents another link to leukemia which not infrequently constitutes the final stage of polycythemia.<sup>202</sup>

The treatment of polycythemia is to remove or destroy the excess of erythrocytes by blood letting, irradiation, phenylhydrazine, arsenic and other drugs.

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<sup>202</sup>Waldman, F. D., and Klauder, J. V. *Acne Urticata Polycythæmia*. Positive Oxidase Reaction in Lesions Microscopically and Microscopically. *Arch. Dermat. & Syph.* 29: 645-650, 1939.

## CHAPTER XXXIV

# DISORDERS OF THE BLOOD AND THE BLOOD FORMING ORGANS

### Hemorrhagic Diseases

The characteristic common to all diseases of the hemorrhagic group is abnormal bleeding. The flow of blood from an injured vessel starts a sequence of mechanisms. The injured small blood vessel contracts slowing down or stopping the bleeding. Macfarlane<sup>329</sup> explains this primary vascular constriction by assuming that the flow of blood removes the dilating histamin like substance released by trauma. Blood platelets then form a clot which is finally reinforced by the formation of fibrin. The vasoconstriction is a quick response which slows the flow of blood sufficiently so that the platelets can collect from the blood and form an adherent thrombus. This clot retracts and closes the wound firmly and permanently. Since the contracted vessels relax after a certain period of time blood would start flowing again and the clot would be pressed out if it had not become firmly adherent and by its power of retraction pulled the walls of the injured vessel together.<sup>330,331</sup> This mechanism of hemostasis may be disturbed in any of its phases. There may be lack of capillary reaction clotting may fail or a combination of both may occur. Abnormal bleeding will result in any case. Furthermore decreased resistance of the capillary wall is an important factor in many hemorrhagic diseases.

In thrombocytopenic purpura lack of capillary contractility and a low platelet count are combined. The bleeding time is prolonged just as it is in thrombocytopenic purpura where the platelet count is normal. In Osler's disease the trouble is completely vascular and restricted to the capillaries. In hemophilia fibrinopenia pseudohemophilia jaundice and hemorrhagic disease of the newborn defective coagulation is responsible in the two latter conditions being combined with capillary dysfunction.<sup>332</sup>

Capillaryoscopic observations<sup>333</sup> suggest that the blood of ecchymoses does not come from the capillaries but from the subcapillary venous plexus. Fresh petechiae have a red color. This is probably due to the presence of engorged very superficial small vessels and a small amount of extravasated blood in the upper layers of the cutis. The combination of vasodilatation and free hemorrhage in the deeper layers produces a bluish lesion.<sup>334</sup>

**Blood Coagulation.** The transformation of fibrinogen a labile colloidal blood protein which is probably formed in the liver or perhaps in the reticulo-

<sup>329</sup> Macfarlane R. G. Mechanism of Hemostasis. Quart. J. Med. 16: 1-20, 1941.

<sup>330</sup> Jürgensen E. Capillarschrankungen (Hockstrungen) bei Purpura, Deutsche Arch. f. klin. Med. 178: 434-64. 1933. Abh. 47: 479.

<sup>331</sup> Peck M. Rosenthal N. and Kuf L. Purpura. Classification and Treatment With Special Reference to Trauma With Snake Venom, Arch. Dermat. & Syph. 55: 631-667. 1937.

endothelial system into fibrin of which the clot mainly consists is only the final phase of the chain of reactions which constitute coagulation. The formation of fibrin from fibrinogen needs an enzyme thrombin which is not present in the circulating blood since the blood would otherwise coagulate in the vessels. If needed it is synthesized from a liver protein called prothrombin and free calcium ions. Naturally the prothrombin too must be held inactive under normal conditions. The activator of the prothrombin is thromboplastin which is held ready in the blood platelets.

The most important methods used to diagnose a hemorrhagic disease are <sup>324,325</sup>

1 The *coagulation time* of the blood. Normal blood coagulates in a test tube in one to five to eight minutes (Lee and White)

2 The *bleeding time*. The skin bleeds from a small cut into the ear lobe for from one to three minutes. The bleeding is recorded by blotting on white blotter every thirty seconds (Duke's method). This demonstrates the capillary reaction to injury.

3 The *capillary resistance*. This is most readily tested by the *tourniquet test* (Leede-Rumpel test). Haden<sup>326</sup> calls the test positive if after placing a blood pressure cuff on the upper arm for three minutes at a pressure of 100 mm. of Hg a crop of petechiae appears below and under the cuff. According to Quick<sup>327</sup> the pressure should be kept for eight minutes midway between the diastolic and systolic pressures. The petechiae which are visible to the naked eye within a circle 5 cm. in diameter drawn on the flexor surface of the forearm with the center 4 cm. below the bend of the elbow are counted after fifteen minutes. The test is considered positive if more than ten petechiae appear. Other tests for capillary fragility based on pinching<sup>328,329</sup> suction<sup>329-330</sup> or perfrigeration with ethyl chloride<sup>331</sup> have not become as widely used as the simple tourniquet test. Madison and Squier<sup>332</sup> and many other investigators consider a positive Leede-Rumpel test a pathological finding of significance. These authors found the test positive in scurvy, severe infections, malignant hypertension, ovarian dysfunction, allergic reactions in the final phase of some malignancies and especially in primary blood diseases. Intradermal injection of 0.1 or 0.2 c.c. of a 1:3000 solution of dried moccasin venom is another method for gauging the capillary resistance.<sup>333</sup> The test is positive when a hemorrhage of 1 cm. or more in diameter appears within one hour at the site of injection.

<sup>324</sup>Kocbawskow, P. W. Zu Frage der Durchlässigkeit der Blutgefäße der Haut, Arch. f. Dermat. u. Syph. 157: 45-480, 1923.

<sup>325</sup>Hammer, F. Hemorrhagische Krankheiten, Handb. d. Haut u. Gk. 2, 2: 512-543, 1933.

<sup>326</sup>van Borselly, F. Ueber die Blutdurchlässigkeit der Haut, München. med. Wochenschr. 77: 946-948, 1900.

<sup>327</sup>Krotzger, E. Allgemeine Dermatologie oder Pathologie der Hautkrankheiten, Berlin, 1906.

<sup>328</sup>Chew, J. S. and Johnson, C. H. Capillary Fragility. A Device for the Study of Capillary Hemorrhage, J. A. M. A. 166: 805, 1928.

<sup>329</sup>Barragán, A. New Sign of Capillary Fragility. Edited by Ethyl Chloride Perfrigeration Test in Case of Orthostatic Purpura, Riv. di clin. med. 41: 263-271, 1940; Ed. 39: 418.

<sup>330</sup>Madison, F. W. and Squier, T. L. Bleeding Due to Capillary Defect, Wisconsin M. J. 30: 31-34, 1940.



4 *Clot retraction time* The clot normally separates from the serum in thirty to sixty minutes. If the platelet count is lower than 70 000 no or in complete clot retraction occurs.

5 *The platelet count* The normal platelet count is 250-500,000

These relatively simple tests are sufficient for the vast majority of cases. For chemical assays of blood components which participate in the process of coagulation see Quick.<sup>340</sup>

### Hemophilia

Hemophilia is a hereditary constitutional lifelong disease characterized by severe bleeding on relatively slight trauma. It becomes manifest only in the male although the daughters of a patient are able to transmit the disorder to their sons. Besides dangerous and often fatal hemorrhages following injuries hemorrhages into body cavities especially joints are common while spontaneous hemorrhages into and from the mucous membranes do not belong to the typical syndrome. Lasting deformities from hemarthrosis are usually present after the age of ten.<sup>341</sup>

The typical laboratory findings in hemophilia are prolonged coagulation time sometimes of more than 48 hours while the platelet count the clot retraction and the bleeding time (from puncture or small incision) are mostly normal. It seems contradictory that the bleeding time from small cuts is normal according to most authors and that at the same time the blood needs so much time to coagulate. This is explainable by the intact capillary constriction and by the fact that hemophilic blood still clots a little when passing over hemophilic tissue.<sup>342, 343, 345</sup>

The presently accepted explanation for the pathogenesis of hemophilia is the resistance of the platelets to disintegrate and to release the thromboplastin. This in turn prevents the release of the prothrombin which is needed for clotting. Why the blood platelets are so resistant is unexplained.<sup>346</sup> A vascular factor consisting of pathological vasodilatation on slight stimuli (Ricker after Gottron<sup>347</sup>) may play a part.

**Dermadromes.**—In contrast to other hemorrhagic diseases hemorrhagic skin lesions are not a dominant feature. There are usually no petechiae and the tourniquet test is negative except during bleeding phases.<sup>348</sup> The patients bruise more easily than normal persons and occasionally show large ecchymoses which require a long time to disappear.<sup>349</sup> Small bruises in hemophiliacs tend to have a hard raised blanched center surrounded by discoloration.<sup>350</sup> Such ring-shaped suffusions may become concentric rings if the central bleeding recurs. If it stops the periphery may continue to extend into the surrounding tissues. Large hematomas of the scalp are often seen. It has already been mentioned that small skin wounds do not bleed excessively. Even minor operations like lancing

<sup>340</sup>Dirch, C. L. Hemophilia, Illinois Medical and Dental Monographs No. 4, University of Illinois, 1937.

<sup>341</sup>Érard-Well, P. Hémophilie. Nouvelles traités de médecine. Publié par G. H. Roger Fournand Vidal and P. J. Trémier, vol. LX, Paris, 1937. Masson & Co.

<sup>342</sup>Bydoch and Fildes. Hemophilia. Treasury of Human Inheritance, Galton Laboratory University of London, Parts V and VI Sec. XIVa, London, 1911. Cambridge University Press.

of an abscess have been done without excessive bleeding. However circumcision tooth extractions small furuncles, vaccination pustules, blows on the nose and biting of the tongue have often caused serious or fatal bleeding. Small injuries in the mouth may develop constantly growing clots which fill the whole mouth and protrude like a huge tongue. Similar growing clots can be seen on the skin. A rare incident is dry gangrene of a foot with spontaneous amputation without bleeding as seen in the case of a boy<sup>200</sup>



Fig 217 — Hemophilia. A small furuncle was followed by for five weeks. The picture shows the crust eight weeks later, depicting hemorrhage which lasted variety of Hæmo Press. Monograph on Hemophilia) (Courtesy Dr G. L. Birch and Uni-

According to some older authors the hemorrhagic tendency decreases in the adult age but the majority of the hemophiliacs bleed to death in childhood sometimes at birth from the umbilical cord. More recently the decrease of the hemophilic tendency in advanced age has been denied.<sup>201</sup> Periods of in-

creased hemorrhagic tendency sometimes alternate with almost normal periods. Spontaneous hemorrhages frequently recur in cycles of three to six weeks. Spontaneous hemorrhages have occurred in the early spring less severe ones in the



Fig 325 — Hemophilia. The patient suffered small cuts in the mucous membrane of the lip. A day later he began bleed and continued for eight days. The swelling of the lip and the large clots made it impossible for the patient to eat, so that he had to be fed liquids through a syringe inserted into his mouth and directed toward the hard palate. The passage of nasal tube is dangerous procedure in hemophiliac. (Courtesy Dr. G. L. Birch and University of Illinois Press. Monograph on Hemophilia.)

fall. Hemorrhages may continue for days and weeks with tremendous loss of blood. The immunity of women is probably not an absolute one since a hemorrhagic tendency especially from the uterus has been claimed in some females.<sup>304</sup>

Émile-Well Opitz and Zweig after Gottron<sup>222</sup> see review of older evidence in Bulloch and Fildes)<sup>223</sup> Birch<sup>224</sup> gives a long list of 'bleeding' females of hemophilic families but she considers none of them as a true case of hemophilia.

No effective treatment of hemophilia is known but injections of blood, plasma human and animal serum and human placental extract may tide the patient over a critical period. Several substances have been prepared from blood



Fig. 324 Hemophilia. Contusion of the foot, which followed an extensive hemorrhage into the right lower abdominal wall and the entire right leg. The foot later showed spontaneous bleeding without the loss of a single drop of blood. Courtesy Dr. H. L. Birch and University of Chicago Press Monograph on Hemophilia.

and plasma which are able to decrease the clotting time of hemophilic blood. In Natelson Lippis a vegetable vitamin and calcium phosphate preparation has been little heard of during the last fifteen years. Many preparations have had the same fate. Pressure applied to a wound tends to increase the surrounding subcutaneous hemorrhage.<sup>225</sup> Several hereditary conditions resembling true hemophilia but differing either in heredity or clinically, have been described. They are all of little dermatological importance.

*Pseudohemophilia* is a rare hereditary disease which unlike true hemophilia occurs in and is transmitted by both sexes. The disease may be carried with out manifestation.

The symptoms are like those of hemophilia but mostly milder especially later in life. The condition may disappear as the patient grows older. Epistaxis, easy bruising and ecchymoses are common but purpura and petechiae have not been seen.<sup>240</sup> Macfarlane<sup>233</sup> has shown in capillaroscopic photography that



Fig. 230.—Hemophilia. Extensive hemorrhage after a blow to the face of the right cheek. (Courtesy Dr. O. L. Birch and University of Illinois Press. Monograph on Hemophilia.)

the capillary loops are partly distorted and do not retract after puncture so that bleeding continues in spite of normal blood platelets, coagulation time, clot retraction and tourniquet test. The bleeding time is prolonged.

*Hereditary (familial) purpura simplex* is much more common than hemophilia. It is more often found in women than in men. The platelet counts, the bleeding, coagulation and clot retraction times are mostly normal but the

<sup>240</sup>Mincot, O. R. A Familial Hemorrhagic Condition Associated With Prolongation of the Bleeding Time. *Am. J. M. Sc.* 175: 301, 1928.

tourniquet tests are often positive.<sup>307-341</sup> The skin manifestations are mainly spontaneous ecchymoses.

In *afibrinogenemia* (pseudo-hemophilia of the German literature)<sup>342-344</sup> an extremely rare anomaly characterized by lack of fibrinogen in the blood all hemorrhagic symptoms of hemophilia including fatal hemorrhage may occur. Coincided ecchymoses around the big joints have been noticed and the patients bruise easily. The blood does not coagulate except on addition of fibrinogen.<sup>344</sup>

### Osler's Disease

Rendu-Osler Weber's disease is a well-defined syndrome which is also known as *angiomatous hereditaria hemorrhagica*.

H. I. Goldstein<sup>345</sup> showed in a series of analyses of the accumulated material that up to 1931 about 110 families had become known in which more than 650 cases of the syndrome occurred. Since then the number of published cases has become larger. There is much discussion about the priority since many cases belonging to the condition had been published before Osler who recognized the triad of telangiectasis, hemorrhage and heredity.<sup>346</sup>

The first visible telangiectases hardly appear before the age of twenty. They appear in crops with a certain predilection to the cheeks and lips. Since the individual lesions rarely disappear spontaneously their number grows with the age of the patient and may reach several hundred.

There are several types of telangiectases. Some of the smaller ones show pulsation under weak glass pressure but most of them are venous.<sup>347,348</sup> There are also small red hemangioma like papules with or without surrounding dendritic vessels. These lesions cannot be blanched by pressure.

The telangiectases develop on the mucous membranes too. The nasal cavity, the tongue and the gums are almost always involved. Hemorrhages have been observed from almost all mucosae from the vagina, the uterus, the bladder, the rectum and other parts of the colon, from the stomach, the bronchi and the larynx, but the nasal septum is by far the commonest source of dangerous

<sup>307</sup>White, L. J. The Hereditary Hemorrhagic Diathesis, Guy's Hosp. Rep. 25: 443-474, 1922.

<sup>308</sup>Davis, E. Hereditary Familial Purpura Simplex, Lancet 1930 2: 11 0-1114.

<sup>309</sup>Davis, E. Hereditary Familial Purpura Simplex. Review of 27 Families, Lancet 1941 1: 144-146.

<sup>310</sup>Barber, F. H. and McAlpin, K. B. Familial Purpura, Report of Two Cases, Am. J. M. Sc. 190: 303-306, 1934.

<sup>311</sup>Modiol, K. Über hereditäre hämorrhagische Diathesen. Acta med. Scandin. 72: 104-112, 1929. 22: 23, 231.

<sup>312</sup>Rabe, P. and Salomon, E. 1. über Eisenstoffmangel im Blute bei einem Falle von Hämophilie, Deutsche Arch. f. klin. Med. 133: 240, 1930.

<sup>313</sup>Ophiz, H. and Froh, M. Über eine neue Form der Pseudo-Hämophilie. Jahrb. f. Kinderh. 94: 274, 1921.

<sup>314</sup>MacFarlane, R. G. A Boy With No Fibrinogen, Lancet 1929, 1: 808.

<sup>315</sup>Goldstein, H. I. Hereditary Multiple Telangiectases, Goldstein's Hereditary Angiomatous With Familial Hemorrhages (Rendu-Osler Weber Disease) Arch. Dermat. & Syph. 24: 283-301, 1932.

<sup>316</sup>Barreck, J. J. Hereditary Hemorrhagic Telangiectases, Wisconsin M. J. 43: 806, 848, 1944.

<sup>317</sup>Weber, F. P. Hemorrhagic Telangiectases of the Osler Type. Case. Brit. J. Dermat. 48: 192, 193, 1936.

<sup>318</sup>Pardo-Castello, V. and Farabee, E. P. Hereditary Multiple Telangiectases, Arch. Dermat. & Syph. 29: 1023-1034, 1930.

hemorrhages. Death either during the attack of untractable epistaxis or by severe secondary anemia caused by the repeated attacks has often been reported but cases without the dangerous hemorrhagic tendency are known<sup>240</sup> Heredity is the third characteristic of the syndrome Unlike hemophilia the condition is not sexbound and it is transmitted by both sexes following a dominant pattern of heredity

Besides changes caused by secondary anemia the blood findings are normal especially with regard to bleeding and coagulation time The affected capillaries have lost their contractility on injury<sup>241</sup> Splenomegaly and swelling of the liver occur frequently<sup>242 243</sup> Scherer<sup>243</sup> observed cirrhosis of the liver in both mother and daughter with Osler's disease This is interesting in view of the vascular spiders which are common in hepatic cirrhosis.

Capillaroscopy reveals excessive richness of surface capillaries and lengthening or tortuosity of the loops<sup>244</sup> Bommer saw aneurysms in great number but never in the retina.

The histology shows the weakness or hypoplasia of the connective and elastic tissue explaining the bulging and vulnerability of the small vessels. The condition must be considered as a systemic, hereditary disorder of the entire connective tissue system<sup>244</sup>

The therapy is mainly limited to the destruction of the individual lesion by cautery This operation reportedly often fails to stop the bleeding Houser<sup>245</sup> and Fitz Hugh<sup>246</sup> advise against blood transfusion if spleen and liver are enlarged

In several patients with Osler's disease some of the telangiectases of the mucous membranes were seen to diminish or disappear entirely on treatment with moccasin venom<sup>246</sup>

### Thrombocytopenic Purpura

Thrombocytopenic purpura is also known as morbus maculosus hemorrhagicus or Werlhof's purpura Its main feature is abnormal bleeding which may occur in any organ the skin almost never being spared All mucous membranes especially those of the nose the mouth the lungs the genitourinary and the digestive tracts may ooze blood in varying degrees of severity Cerebral and adrenal hemorrhages occur The onset is often sudden without any premonitory symptoms. The course may be hyperacute acute chronic or intermittent The disease may terminate in complete restitution or in death from hemorrhage or from aplastic anemia caused by the repeated attacks. No

<sup>240</sup> Jibradt W Erfolgriche Lebertherapie bei einem Fall von Telangiectase haemorrhagica hereditaria (Osler Disease) mit Leberstörung Arch f. Dermat. Syph 166 34-40, 1932.

<sup>241</sup> Jibradt W A typische diffuse Skleroderma mit Oslerischem Syndrom und Leberstörung Dermat. Wchnschr 66 973-978 1934

<sup>242</sup> Rosenthal Oslerische Krankheit, Kbl 48 720 1932

<sup>243</sup> Fitz-Hugh, T J Splenomegaly and Hepatic Enlargement in Hereditary Hemorrhagic Telangiectase, Am J M Sc 191 961-968 1931

<sup>244</sup> Va Dognart, L and Scherer H J Hémangiomatose familiale de Rendu-Osler et cirrhose hépatique Ann de méd 38 290-300, 1928

<sup>245</sup> Rosenthal F and U na, P Ueber das Wesen der Oslerischen Krankheit Klin. Wchnschr 12: 645-647, 1933

<sup>246</sup> Houser K. M Hereditary Hemorrhagic Telangiectase, Ann. Otol. Rhin. & Laryng. 42 731 734, 1934

age is immune but children and adolescents especially girls in puberty are more likely to become afflicted and their cases are more often acute. The typical blood findings are low platelet count and increased bleeding time up to ninety minutes. The coagulation time is normal or only moderately increased but the clot does not retract. The coagulated blood remains in a jelly like condition. The tourniquet test is positive. Anemia and abnormalities of the leukocytic picture are absent.<sup>262</sup> The spleen is often enlarged and tender.

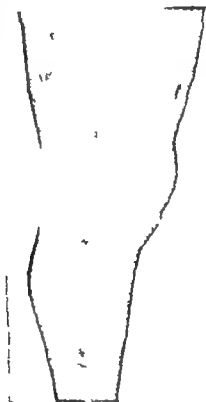


Fig. 251.—Thrombocytopenic purpura. Abdominal tenderness. (Courtesy Dr. Erich Urbach.)

Thrombocytopenic purpura is either an entity of its own, the cause of which is unknown, or it is caused by a known factor such as infection, blood dyscrasia, poisoning or liver disease. E. Frank called the idiopathic type essential thrombopenia (thrombocytopenia) to separate it from similar hemorrhagic diseases secondary to other conditions. There is no dermatological difference between these two groups. Essential thrombocytopenia is a rare disease. Only about 179 cases were counted in 275,000 admissions in two American and one European hospitals.<sup>263</sup> These figures probably include some secondary cases. The belief is gaining ground that, owing to the shortcomings of the present diagnostic means, create what is known as essential thrombopenic purpura.

<sup>262</sup>Rosenthal, N. Cause and Treatment of Thrombopenic Purpura. J. A. M. A. 112: 101-108, 1939.



**Dermadromes**—The cutaneous purpura appears in crops of varying abundance and on slight local trauma. A ready tendency to bruise particularly over the shins and knees is often the first intimation of the disease.<sup>200</sup> The purpuric spots frequently appear first on the legs and they may be restricted to the legs in less severe cases. More often the crops gradually cover the whole body. Petechiae and suffusions are usually seen simultaneously. The mixture of both types of hemorrhagic lesions in the same patient is considered a characteristic feature of the morbus Werlhof<sup>201</sup> but this should not be taken too literally. Some cases at least at certain times, show only mucosal lesions. The fresh suffusions are not always purely hemorrhagic. When they appear they some



FIG. 323.—Acute purpura. It is thrombocytopenia.

times have an *urticarial* character being pink and elevated and show their hemorrhagic nature more clearly only later. Such cases which are on the border line of the anaphylactoid form of purpura are rare. They may be associated with edema of the ankles. Suffusions can easily be produced by gentle flicking, bumping or pinching. They sometimes appear on areas which are exposed to pressure e.g. the buttocks or the shoulders. The petechiae can be provoked by increased venous pressure by coughing, pressing during a bowel movement etc. They appear as deep purple sharply outlined pin point or lentil sized spots, sometimes lined up in streaks from scratches.

Change from the horizontal to the upright position may produce purpuric lesions. This phenomenon known as orthostatic purpura is often marked in patients who are just recovering from an attack of thrombopenic purpura. It can be observed in other types of purpura too.

Purple or black spots or suffusions especially of the gums and of the oral or pharyngeal mucosa are quite common<sup>307</sup>. This diapedetic bleeding from the mucous membranes may create a very serious condition.

**Pathogenesis.**—Thrombopenia and abnormal bleeding are the outstanding signs of Werlhof's disease. Since the blood platelets are born in the bone marrow and die in the reticulo-endothelial system especially the spleen, their population in the blood can be influenced from both ends. Depression of the bone marrow by bacterial and other poisons, by radiant energy, carcinomatosis and other local processes may thus result in the same thrombopenic and purpuric effects as hyperactivity of the spleen. The spleen may be thought of as devouring the platelets or as exerting a depressing influence on the megakaryocytes in the bone marrow possibly by means of a hormonal mechanism. (For discussion of the experimental evidence see Quick<sup>308</sup>). It has long been observed that however striking the thrombopenia in Werlhof's purpura may be, no definite parallel between platelet count and purpura exists. Sometimes bleeding occurred in moderate thrombopenia, and in some cases purpura did not appear with very low platelet numbers,<sup>304</sup> or the platelet count decreased only after the hemorrhage<sup>301</sup>. Macfarlane<sup>303</sup> showed in capillaroscopic photographs that the injured capillaries did not retract in thrombopenic purpura. These and many other observations show that the vascular reaction, more precisely the lack of vasoconstriction after injury is an important factor. Quick<sup>309</sup> tried to connect the platelet and the vascular theories. The capillary dilation is caused by histamine and one of the functions of the platelets is to remove this agent which is formed in excess. In carrying out this task the platelets are rendered more susceptible to agglutination and lysis. This hypothesis which is based on considerable evidence would explain vasodilation as well as loss of platelets. The spleen or the reticulo-endothelial system is possibly a major source of the histamine which kills off the platelets. The opinion that allergy plays a part in thrombopenic purpura is gaining favor and is expressed in the tendency to remove the borderline between thrombopenic and nonthrombopenic purpura. The main reasons for an allergic theory of thrombopenic purpura are based on the great number of cases which have been observed after prolonged and repeated medication with anaphenamine, gold<sup>309</sup>, sedormid<sup>306</sup>, quinine, nirvanol and after ingestion of cow's milk<sup>306</sup> and other foods. Infections for example pertussis have caused thrombopenic purpura so have blood transfusions.<sup>307-304</sup>

<sup>307</sup>Walton-Williams, K. The Facial Lesions of Purpura, *J. Laryng. & Otol.* 53: 181-186, 1933.

<sup>308</sup>Roskam, J. Purpura hémorragique et thrombopénie. (Étude expérimentale). Pathologie du Syndrome hémorragique engendré par l'administration de sérum antiplaquettes, *Sang.* 3: 170-189, 1934. *Id.* 48: 400.

<sup>309</sup>Hedman, E. H. Purpura Haemorrhagica Caused by Gold and Arsenical Compounds. Two Cases, *Lancet* 3: 74-77, 1933.

<sup>304</sup>II by H. M. Purpura From Sedormid, *J. A. M. A.* 113: 674-678, 1939.

<sup>303</sup>Landesberg, M. Purpura nach K. ähnlich, *Zechr. f. Kinderh.* 39: 589, 1921.

<sup>302</sup>Triantafyllou, H. N. Morbus Werlhofii mit allergischer Reaktion of mütterliches Blut der stillenden Mutter, *Zechr. f. Kinderh.* 51: 566-578, 1923.

<sup>301</sup>Quayle, T. H. and Madson, F. W. Purpura and Food Allergy, *J. A. M. A.* 100: 402, 1930.

<sup>300</sup>Patrick, A. J. J. Thrombopenic Purpura and Other Hemorrhagic Diseases, *Am. J. M. Sc.* 191: 752, 1936.

No matter what the final conception of the pathogenesis of hemorrhagic purpura will be the importance of the capillary factor is established

**Treatment**—The most important step toward successful treatment is to find out whether there exists a causal infection poisoning blood-dyscrasia or malignant disease which may be treated. In the remaining idiopathic or essential cases the tendency to remissions and spontaneous healing make an evaluation of any therapeutic procedure in thrombopenic purpura difficult. However since Kaznelson<sup>284</sup> in 1916 based on E. Frank's work first advocated splenectomy the number of successful operations has become so large that the method is now generally considered the only means that can be relied upon when all other therapy fails.<sup>285</sup> Many large series have been reported so that the error from spontaneous healing<sup>286</sup> is now small. The postoperative mortality is seven per cent<sup>287, 288</sup> to ten per cent<sup>289</sup> in chronic cases. In Pemberton's series of fifty-seven operations (Mayo Clinic) sixty-three per cent were permanently cured and almost all the others improved. Pemberton<sup>289</sup> feels that splenectomy is indicated in the moderately severe cases with a definitely established diagnosis. Early and mild cases do not need splenectomy. They can be treated with blood transfusions and small doses of x ray to the spleen. However splenectomy, if indicated, should not be delayed too long<sup>290</sup> because the operative danger increases as the condition of the patient becomes weaker. Most authors advise against splenectomy in acute cases. Kaznelson<sup>284</sup> in a review of 168 cases estimates the postoperative mortality in acute cases to be as high as 20 to 30 per cent and in juvenile patients of the acute group 35 to 50 per cent. Three out of four patients with acute thrombopenic purpura who had splenectomy died but four other patients of the same category who were treated with blood transfusions only died too.<sup>291</sup> The postoperative mortality has come down to 13 per cent in the acute cases (Brown and Elliott after Quick<sup>292</sup>) but splenectomy in children must still be considered as very dangerous. Smears from extirpated spleens usually do not show pathologic changes. Only occasionally are the splenic blood platelets increased.<sup>293</sup>

X-ray treatment of the spleen has a hemostatic effect in many types of hemorrhagic disease. Considering the relatively high mortality of splenectomy especially in juvenile and acute cases this method deserves a trial. In a review of 45 cases treated with x ray Vaughan<sup>294</sup> found 25 cures and 20 failures. About 25 per cent of the cases were acute ones which were almost all listed as cured.

<sup>284</sup>Kaznelson, I. Versuch inden der hämorrhagischen Diathese bei einem Fadr. an essentialer Thrombopenie. Frank nach Villers Irritation pleurocyter hämolytische Purpura. Wien klin. Wochenschr. 29. 48. 1909.

<sup>285</sup>Jones H. W. and Tors. op. cit. The Treatment of Purpura Hemorrhagica. J. A. M. A. 1901: 22-23. 1933.

<sup>286</sup>Ellison, E. and Ferguson, L. B. Splenectomy in Purpura Hemorrhagica. Ann. Surg. 94: 90-99. 1932.

<sup>287</sup>Pemberton, J. de J. The Diagnosis and Treatment of Purpura Hemorrhagica. Am. J. Surg. 34: 793-806, 1934.

<sup>288</sup>Kaznelson, I. Zur Behandlung der essentialen Thrombopenie. Arch. f. klin. Chir. 1901: 794-806, 1931.

<sup>289</sup>Vargallo, E. R. Treatment of Purpura Hemorrhagica. Report of 23 Cases. Am. J. Surg. 23: 93-95, 1933.

<sup>290</sup>Vaughan, J. M. Treatment of Thrombocytopenic Purpura. Brit. M. J. 2: 843-844, 1937.

Other reports are inconclusive because of small numbers or not comparable because of great differences in technique.

Rudin<sup>1872</sup> and also Mettler and Stone<sup>1873</sup> believe that roentgen-radiation is valuable (8 cases) in thrombopenia. Doses at 200 r per sitting applied to the spleen with low intensity and heavy filtration are recommended. About six treatments may be given with three days interval. The platelet count has been seen to rise after the first treatment. Most of the chronic cases are now operated upon the cases with poorer prognosis being left to other methods.<sup>1871, 1877</sup> X-ray therapy is less reliable than splenectomy but practically without danger. It may well tide a patient over a critical phase.

Blood transfusions are of great but only palliative value. Rosenthal<sup>1888</sup> sees no value in repeated small transfusions. Vitamins C and B parathyroid extracts and Stryphnon<sup>1878</sup> have been advocated. Moccasin snake venom<sup>188</sup> is of some palliative value in chronic cases.<sup>1880</sup>

### Schönlein-Henoch's Non thrombocytopenic or Anaphylactoid Purpura

After separating the thrombocytopenic purpura a group of purpuras remain which—though not without exceptions<sup>1882</sup> has normal platelet count normal bleeding and coagulation times and normal clot retraction. Usually the tourniquet test is positive.<sup>1889</sup> Allergy and infection have been increasingly found to be significant in their pathogenesis. The combination with other symptoms which are well established allergic phenomena like urticaria angioneurotic edema and swelling of the joints is reflected in the term anaphylactoid.<sup>1882</sup> Today the group would probably be called allergic purpura. However there are many cases in which no allergic or infectious cause can be detected.

In Schönlein's purpura as the anaphylactoid purpura has been and still is called the urticarial component is a characteristic feature. Glanzmann<sup>1882</sup> used the term purpura urticaria for raised white or pink, small or large wheals. The petechiae often develop within the urticarial and slightly inflammatory lesions. While the urticarial element quickly disappears, the hemorrhagic part stays and undergoes the well known changes.

<sup>1872</sup>Rudin, H. Jr. Successful Treatment of Essential Thrombopenia With Hemorrhage by Roentgen Rays. J A M A 1927 2119-2120 1929.

<sup>1873</sup>Mettler S. R. and Stone R. B. Effect of Roentgen-Ray Irradiation on Platelet Production in Essential Thrombocytopenia. Am J 31 No 181 794-807 1936.

<sup>1878</sup>Hippe U. and Kochmann R. Die Behandlung der thrombopenischen Purpura im Kindesalter mit Röntgenstrahlungen der Milz. J kreb f Kinderh. 1936: 302-306 1937.

<sup>1879</sup>Kistner A. J. Harrison K. M. J. and Thomas C. R. Purpura Hemorrhagica With Special Reference to Course and Treatment. J A M A 188 1170-1176, 1937.

<sup>1880</sup>Hatfield, S. La roentgenotherapie nella malattia sindrome essoragica. Radiol med 19: 772-830 189-223 1933.

<sup>1882</sup>Hist, W. Ueber die Anzeigen zur Röntgenbehandlung bei Kinderkrankheiten und über die Erfolge derselben II. III. Mittheilung med Wchnscr 1931 II 1219 1222.

<sup>1883</sup>Klein R. Neue Behandlung von thrombopenischer Purpura. Klin Wchnscr 1936 I 823-877.

<sup>1884</sup>Tracy S. M. and Rowenhal W. Effect of Moccasin Snake Venom (Atractodes platyrus) in Hemorrhagic Conditions. J A M A 184 680, 1933.

<sup>1885</sup>Glanzmann, E. Schönlein-Henoch Purpura. Report of Case With Review of the Literature. Clin North America 12 408-8 1 1935.

<sup>1886</sup>Glanzmann, E. Purpura Palmarum. Schweiz med Wchnscr 67 429-430 1937.

Erythema nodosum and erythema multiforme like eruptions have been observed. The pleomorphic character of the lesions is supposed to be an outstanding feature<sup>11,236</sup>. The lesions appear in crops predominantly over the lower legs. Less frequently the other parts of the body are involved. The face the bends of the large joints and the palms and soles usually remain free<sup>112</sup>. The crops follow each other in intervals of days or weeks. Recurrences have been observed years after apparent healing.

The spring of the year seems to favor the first outbreak as well as recurrences. The term purpura (peliosis) rheumatica refers to the combination of purpura with painful mostly serous exudations into the joints. They have nothing to do with rheumatic fever.

*Henoch's purpura* is an anaphylactoid purpura with acute hemorrhagic intestinal symptoms. Heartburn epigastric discomfort abdominal colic nausea and vomiting melena constipation or more often diarrhea with bloody stools and other symptoms of acute abdominal disease are usually present and have not infrequently led to a diagnosis of appendicitis or intussusception with subsequent laparotomy<sup>237</sup>. Purpuric skin lesions in acute abdominal conditions especially in children should make the possibility of Henoch's purpura enter the physician's mind. There are showers of petechiae on the skin<sup>112</sup> and polymorphous skin lesions similar to those in Schönlein's purpura to which Henoch's purpura is related. Unfortunately the purpura often follows the abdominal symptoms by several days which complicates the matter and explains the diagnostic errors.

The allergic character of many cases of Schönlein's and Henoch's purpura has been demonstrated<sup>238</sup>. Improvement after elimination of wheat<sup>239</sup> eggs and wheat<sup>240</sup> and a number of other items like pork milk, potatoes, chicken etc.<sup>238,240</sup> has been observed. Allergic diseases in the family hay fever in infantile eczema and preceding allergic diseases are more common than one would expect<sup>240</sup>. The relationship to urticaria angioneurotic edema joint swellings and the resemblance to serum sickness has often been emphasized. Accompanying infection is just as common. Tuberculosis tonsillitis<sup>241</sup> scarlet fever<sup>242</sup> prostatitis (O'Leary in discussion of Carr and Zeisler<sup>243</sup>) malaria tropica<sup>244</sup> may be mentioned as a few examples.

*Purpura fulminans* is a rare fatal hemorrhagic disease which occurs in severe mostly septic infections. The patients are almost always children. While infections with pneumococci as well as scarlet fever and measles have occu-

<sup>236</sup>Alperstein, D. D.: Allergic Purpura and Acute Abdominal Symptoms. *M. Rec.* 124: 218-222, 1941.

<sup>237</sup>Kahn, I.: Henoch's Purpura Due to Food Allergy. *J. Lab. & Clin. Med.* 13: 823-826, 1929.

<sup>238</sup>Barthelme, F. L.: Allergic Purpura. *J. Allergy* 2: 170-171, 1930.

<sup>239</sup>Alexander, H. L. and Eysmann, O. H.: Allergic Purpura. *J. A. M. A.* 88: 2092-2094, 1929.

<sup>240</sup>Eysmann, C. H.: Henoch's Purpura. *South. M. J.* 28: 34, 1935.

<sup>241</sup>Coke, H.: Two Interesting Cases of Purpura. *Brit. M. J.* 2664: 525-527, 1951.

<sup>242</sup>Pratt, T. A. and Frew, H. W.: Purpura Fulminans Following Mild case of Scarlet Fever. *Brit. M. J.* 3500: 596-598, 1930.

<sup>243</sup>Carr, M. E. and Zeisler, E. P.: Recurrent Chronic Purpura. *Arch. Derm. & Syph.* 24: 702-703, 1931.

<sup>244</sup>Barthelme, F. L.: Zwei Fälle von Malaria mit Henoch-Schönlein bzw. Weithofener Purpura. *Dtsch. B.* 265-267, 1927. *Id.* 27: 429.

tionally been followed by fulminating purpura the majority of the cases were observed in the course of meningitis.

The ecchymoses in purpura fulminans occupy large areas, e.g. entire extremities and sometimes almost the whole skin. These giant lesions develop very rapidly often in a few hours. The involved areas are sometimes entirely black. A certain symmetry of the purpuric lesions is striking in some cases. The platelets, bleeding time, coagulation time, clot retraction and fibrinogen were normal in Glanzmann's case. The autopsy findings are mostly negative.<sup>221</sup> This is not the case in a group of fulminating purpuras which now can well be separated and which is known as the *Waterhouse-Friderichsen syndrome*.<sup>222,223</sup> Only about sixty cases have become known since Marchand (according to Glanzmann<sup>222</sup>) in 1880 first observed a case of this kind. The terminology should give credit to Little<sup>224</sup> who in 1901 ten years before Waterhouse and seventeen years before Friderichsen published twelve cases, the greatest contribution of a single author.

The syndrome occurs mostly in children younger than one year but it has been seen in adults.<sup>225</sup> The onset is very sudden often with abdominal pain and vomiting, moderate fever and flushed face. The patient soon becomes stuporous this may be mistaken as healthy slumber.<sup>226</sup> After ten to twelve hours cyanosis which may alternate with ashen gray pallor is striking. In this stage showers of petechiae may appear over the whole body. The purpuric spots increase rapidly sometimes under the very eyes of the observer. They may coalesce and produce a blotchy appearance. On the buttocks, back and extensor surfaces of the arms they may look like postmortem lividity. The rash remains until death. Rarely the petechiae stay small. According to Aegerter<sup>226</sup> no skin lesions showed in thirteen out of fifty seven cases.

Headache and other symptoms of the nervous system, profound weakness, spiking temperatures from subnormal to 108°F, low blood pressure and circulatory disturbances are often mentioned. Cervical rigidity is usually absent. Almost all patients died within a day or two. The diagnosis is rarely made antemortem. Leukocytosis is mentioned in seven cases.<sup>227</sup> In two cases<sup>228,229</sup> the platelet counts were extremely low. In two others, normal. Most of the other cases do not mention hematological findings.<sup>230</sup> Coagulation and bleeding time have been found normal several times. Hypoglycemia and elevation of nonprotein nitrogen of the blood has been described.<sup>231</sup> At autopsy the out-

<sup>221</sup>Waterhouse R. A Case of Adrenal Apoplexy. *Lancet* 1911, 1: 577-578.

<sup>222</sup>Friderichsen, C. Nebennierenapoplexie bei kleinen Kindern. *Jahrb. f. Kinderh.* 87:100-121 1918.

<sup>223</sup>Glanzmann, E. Beitrag zur Klinik, Hämatologie und Pathologie des Syndroms von Waterhouse-Friderichsen (Nebennierenapoplexie bei kleinen Kindern). *Jahrb. f. Kinderh.* 129: 49-82 1933.

<sup>224</sup>Little E. O. Cases of Purpura, Ending Fatal. Associated With Hemorrhage Into Supratentorial Capsules. *Brit. J. Dermatol.* 13: 443-457 1901.

<sup>225</sup>Thomas II B. and Leishart, O. D. Septicemia and Purpura With Adrenal Hemorrhage in the Adult. *J. A. M. A.* 123: 894-900, 1944.

<sup>226</sup>Aegerter E. K. The Waterhouse-Friderichsen Syndrome. A Review of the Literature and Report of Two Cases. *J. A. M. A.* 194: 1718-1719, 1926.

<sup>227</sup>Levinson, R. A. Waterhouse-Friderichsen Syndrome. Case With Autopsy Findings. *J. Pediatr.* 11: 306-311 1937.

<sup>228</sup>Usher S. J. Waterhouse-Friderichsen Syndrome. *Canad. M. A. J.* 23: 232, 1935.

standing finding in 95 per cent of the cases was destructive bilateral adrenal hemorrhage. Often no adrenal tissue could be made out.

It is now certain that most of these cases are caused by meningococci infection probably with a massive invasion of meningococci into the blood stream. Just as in other rashes of meningococci disease meningococci have been found in the purpuric lesions.<sup>1299,1300</sup>

*Purpura annularis telangiectodes* Majocchi and Schamberg's disease, two related purpuric skin diseases, have some internal relationship. (See Polycythemia.)

Recently E. Davis<sup>1301</sup> has given a statistical analysis of 500 consecutive cases of purpura. This large series provides an idea of the frequency of the various types of purpura. The diagnosis of purpura simplex was made in 15 per cent. Schönlein's purpura in 2 per cent. Henoch's in 0.4 per cent. hereditary familial purpura simplex 15 per cent. primary thrombocytopenia 0.8 per cent. hemophilia 0.2 per cent and pseudohemophilia, familial or nonfamilial in 1 per cent. The rest (63 per cent) was grouped under the many types of symptomatic purpuras in infections, poisonings, etc.

<sup>1299</sup>M. Leas, H. and Coffey J. Erythema Purpuric Meningococcus Bacteraemia I. Early Life. Diagnostic Value of Rashes From Purpuric Lesions. *Ann J Dis Child* 42: 1042 (1931).

<sup>1300</sup>Latter O. A di. caso di purpura fulminant. *Pediatrics (Riv)* 29: 372-3 (1931).

<sup>1301</sup>Davis E. Purpura of Child, 500 Cases, *Lancet* 1932 2: 160-161.

## CHAPTER XXXV

### DERMADROMES OF INTERNAL CANCER

Internal cancer may manifest itself on the skin by *metastases* by *nonspecific dermadromes* and by *acanthosis nigricans*.<sup>3003</sup>

**Cutaneous Metastases.**— It can generally be said that only mammary cancer in advanced stages as well as occasionally after the operation of cases on the borderline of operability reach the skin frequently by direct extension by operative implantation or by lymphatic metastases.

The contiguous metastases appear as painless nodules which grow rapidly and if dense enough coalesce into large hard masses which may surround the chest wall like armor (Cancer en cuirasse). Sometimes the diffuse invasion of the skin forms an evenly red sharply and jaggedly outlined area of inflammatory cancer which is known as erysipelas carcinomatosum.

Skin metastases from visceral cancers are rare probably occurring not more often than in 1<sup>per cent</sup> to 3 per cent.<sup>3004</sup>

Since there is no flow of lymph directed from the viscera toward the skin the metastases are likely to originate from a primary lesion or still more often from secondary cancers in the lungs<sup>3005</sup> or in the liver. This fact accentuates the ominous significance of all skin metastases of visceral cancer.

Adenocarcinoma of the stomach occasionally produces an outcropping of hard mostly red nodes scattered in moderate numbers over the skin. Firm scleroderma-like plaques in the skin have also been seen.<sup>3006, 3007</sup> Dermal secondaries of hypernephromas, prostatic or breast<sup>3008</sup> cancers, have been found in the scalp suggesting sebaceous cysts<sup>3007</sup> or turban tumors.<sup>3007</sup> The upper abdomen and the umbilicus have relatively often been seen to develop metastatic growths originating from the stomach, ovary or uterus. They are direct subsidiaries of metastatic nodules in the liver from which they travel through the ligamentum teres.<sup>3004, 3009</sup>

Rectal carcinomas may develop sessile or pedunculated metastases about the buttocks.<sup>30</sup> Only a few cases of cutaneous lesions from ovarian carcinoma have been reported.<sup>301</sup> Several of the cases showed firm plaques or confluent nodules in an edematous purplish brown skin which were not very suggestive of metastatic cancer. The lesions resembled erysipelas or more correctly the

<sup>3003</sup>Kothman, Deber Haut erkrankungen bei bösartigen Geschwülsten innerer Organe. Arch. f. Derm. Syph. 109: 90-123 1923.

<sup>3004</sup>Walther H. E. Metastases of Cutaneous Carcinoma and Secondary Skin Tumors, Schweiz. med. Wchnsch. 71: 904-1003, 941.

<sup>3005</sup>Gates, O. Cutaneous Metastases of Malignant Disease, Am. J. Cancer 20: 715-730, 1927.

<sup>3006</sup>Berk, S. C. Epithelioma Handb. d. H., Ok. 12, 3: 395-403 1912.

<sup>3007</sup>Bock, W. Das metastatische Carcinom der Haut im Anschluss an Carcinom innerer Organe, Arch. f. Derm. Syph. 179: 237-274 1930.

<sup>3008</sup>Rosenbaum E. Metastases of the Scalp Simulating Turban Tumors, Arch. Derm. & Syph. 61: 636-648, 1910.



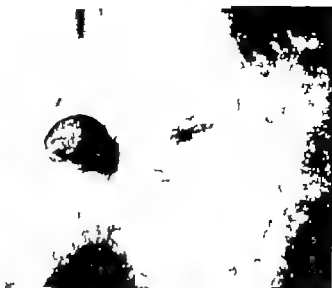


Fig. 332.—Osteocyst metastases from cancer of the stomach.



Fig. 334.—Skin metastases from cancer of the stomach.

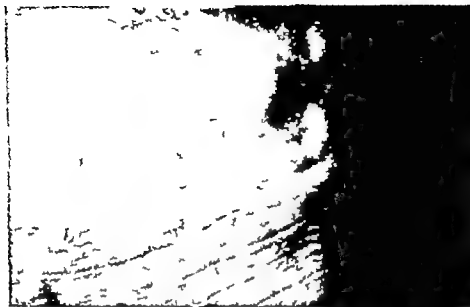


Fig. 335.—Lymphomarcosis cutaneous metastases. Forehead.



Fig. 336.—Skin metastases from lymphomarcosis.

erysipelas carcinomatosum of the breast. The biopsy, however, revealed metastatic ovarian carcinoma. Bronchial carcinomas metastasize to the skin relatively often.<sup>240</sup>

A rare event is the hematogenous spread of a cancer developing from the epithelial lining of an *osteomyelitic sinus*. Crops of metastatic nodules have appeared in the skin of the upper arm after the amputation of an osteomyelitic finger.<sup>241</sup>



Fig. 337. Congested veins in carcinoma of the esophagus.

Lymphosarcoma and melanosarcoma are probably more apt to metastasize to the skin than the other more common cancers. They both form cutaneous and subcutaneous nodules or plaques which in some cases appear on the surface in enormous numbers. The metastases of melanoma are in one out of three cases entirely or partially pigment free (amelanotic) the melanotic character of the cells being demonstrable only by the positive dopa reaction.<sup>242</sup>

<sup>240</sup>Stewart, J. J., Obermayer M. E. and Woodhändler H. Cutaneous Metastatic Carcinoma Originating From Osteomyelitic Cavities Arch. Dermat. & Syph. 41: 545-550, 1940.

Conclusions with regard to the *site of a primary tumor* from the distribution or clinical appearance of skin metastases are less reliable than the pathologic picture.

The skin does not seem to offer a good roll for the cancerous seeds. Skin nodules have been seen to disappear *spontaneously*<sup>300,301</sup> and they usually appear quite *radiosensitive* this can be interpreted as a lack of vitality. A few hundred roentgen units may make them disappear but of course there is no more than palliative benefit for the patient from treating metastases. However it is not true that cutaneous metastases indicate a particularly fast rate of growth of the primary tumor or that they herald approaching death. The patients may still live many months or even years.<sup>300,301</sup> Three years of life have been recorded in a case of adamantinoma of the mandible after distant metastases had appeared on the temple.<sup>300</sup> Three to six months is the average time a patient will live after the appearance of skin metastases.

**Nonspecific Exanthema.**—A still rarer dermatome of internal cancer is the *nonspecific exanthem*. These eruptions range from simple pruritus and prurigo-like eruptions with hyperpigmentation to bullous multiform and eczematoid rashes. Typical dermatitis herpetiformis<sup>302</sup> lupus erythematosus acutus pellagroid and exfoliative dermatitis<sup>303</sup> generalized urticaria<sup>304</sup> purpura,<sup>305</sup> and purpuric dermatitis with widespread superficial necrosis are on record.<sup>300,305</sup> Thrombocytopenic purpura<sup>306</sup> may be caused by massive invasion of the bone marrow by metastases. In some cases<sup>307</sup> a generalized polymorphous exanthem was seen in x-ray treated malignancies of the mouth and neck. Drug eruptions from barbiturates are difficult to rule out in some of these instances.

The rashes especially pruritus, may precede subjective or objective signs of cancer and they may disappear after successful removal of the neoplasms.<sup>305</sup> The peculiar tendency to multiple peripheral thromboses and short clotting time in pancreatic cancer have been mentioned (see pancreas). The exanthems in internal cancers are interpreted as reactions to metastasized tumor cells which have been destroyed by cutaneous defense mechanisms.<sup>305</sup>

Diffuse deep *bluish-black discoloration* of the face neck and hands together with melanuria is a case of widespread metastases of a malignant melanoma was

<sup>300</sup>Bisary A. Horowitz A. and Miger A. Eruptions cutanées métastatiques de la peau. Bull. Soc. franç. de dermat. et syph. 69: 129-130, 1933.

<sup>301</sup>De Rola. Cancer de la langue et métastases cutanées. Sch. etz. med. Wchnsch. 1928, II 1051-1060.

<sup>302</sup>Kaufman-Wolf. 31. Haut metastasen im Anschluss an Karzinom innerer Organe. Arch. f. Dermat. Syph. 134: 700-743, 1933.

<sup>303</sup>Schwartz. Erythema multiforme und Erythema nodosum. Mbl. f. Gynäk. 87: 94-99, 1932.

<sup>304</sup>Reich, E. Endogenous Allergy. Arch. Dermat. & Syph. 68: 687-712, 1943.

<sup>305</sup>Stillman, B. O. Complications of Malignant Tumor with Purpura Hemorrhagica. II. Clin. North America 16: 1833-1875, 1931.

<sup>306</sup>Recker A. W. Kahn, D. and Rothman, R. Cutaneous Manifestations of Internal Malignant Tumors. Arch. Dermat. & Syph. 48: 1008-1040, 1942.

<sup>307</sup>Bloom, K. Über symptomatische Thrombopenie bei Magenkarzinom. Med. Klin. 24: 1900-1905, 1929.

<sup>308</sup>Loew, L. and Camiel, M. R. Exanthem Complicating Neoplastic Disease. 4 Cases. Am. J. Roentgenol. 43: 847-856, 1940.

seen by Odel, Montgomery, and Horton<sup>300</sup>. The authors assumed involvement of the adrenal glands and chromaffin tissue.

The eruptive appearance of senile hemangiomas (ruby points) in relatively young persons has been *disproved* to be suggestive of visceral cancer.<sup>330</sup> Schridde<sup>301</sup> claimed that the occurrence of dark, pigmented coarser hairs of dull surface especially on the temples but also in the eyebrows and beard were indicative of cancer. They were even found among blond and gray but not among red hairs. This claim still lacks confirmation.



Fig. 324.—*Acanthosis nigricans*. (Courtesy Dr. M. Jomier.)

*Acanthosis nigricans* is a dermatosis of remarkably uniform appearance. The disease is rare; about 400 cases have been recorded since S. Polltzer<sup>302</sup> in collaboration with P. G. Unna published the first case in 1890 (see also Polltzer<sup>303</sup>). The significant elements of the gross skin changes are a characteristic distribution, papillary hypertrophy, hyperpigmentation and hyperkeratosis. The sites of predilection are the axillae, the nape of the neck, the genitals, the inner

<sup>300</sup>Odel, H. M., Montgomery, H. and Horton, B. T. Diffuse Melanosis Secondary to Malignant Melanoma, *Proc. Staff Meet. M. Y. C. H.* 13: 742-747 1937.

<sup>301</sup>Schridde, H. Krebshaare. *München med. W. hsehr.* 69: 1505-1506 1922.

<sup>302</sup>Polltzer, S. In *Atlas der Hautkr.* 10: 1890.

<sup>303</sup>Polltzer, S. *Acanthosis Nigricans*, *J. A. M. A.* 53: 1308-1373 1909.

thighs the elbow bends, the umbilicus the perianal region and the dorsa of the hands and feet. In some cases the lips the anterior neck the areolae of the nipples and large areas of the trunk may also be affected. There is almost in all cases, marked symmetry provided the picture is fully developed.

The affected skin is densely covered with mostly smaller than pea-size sessile nodules with a more or less rounded top. Many of them especially in the axillae and on the nape are crowded into rows or small groups and separated by the natural furrows of the skin. Among the great number of little papules is scattered a much smaller number of larger ones forming a picture comparable to the fungi form papillae among the filiform papillae of the tongue. In the folds cauliflower or cock's comb resembling growths have been observed.

The color of the lesions varies from gray slate or yellow to all shades of brown and black. The melanosis often extends beyond the papillomatous area. Sometimes gross hyperpigmentation is missing the lesions then having a yellow orange hue. Depigmentations within the darkened areas are due to inflammation. Scattered nevus-like, hyperpigmented lesions in apparently unaffected skin are frequent concomitant efflorescences which may appear in great numbers.<sup>222</sup> Scaling dryness, or palpable roughness, as gross expressions of hyperkeratosis are present but are not prominent features. The palms and soles are often hyperkeratotic,<sup>223</sup> but they remain free of hyperpigmentation. Pruritus is sometimes present.

The disease starts gradually most often under the arms and progresses slowly. The pigmentation is increased by exposure to light the papillary hyperplasia by friction and maceration.

The oral mucosa and the transitional skin of the lips and of the vulva participate in the papillary hyperplasia in about one half of the cases. The dorsum of the tongue may take on a furrowed appearance resembling lingua plicata and the papillae may be enlarged and rough like those of a cat's tongue. Even thin spines have been described.<sup>224</sup> Similar papillary or granulated surfaces may be seen on the palate the line along the bite on the buccal mucosa, the epiglottis and even in the larynx. Mucosal pigmentation is rare but it has been observed often enough to discredit its absence as being a distinguishing characteristic against Addison's disease and other melanoses. The esophagus,<sup>225</sup> the rectum and the lower part of the vagina often participate in the process.

The hair is usually destroyed in the affected areas.

The nail beds may be pigmented and the nails longitudinally grooved.

The histopathology reveals enlarged and elongated papillae, hyperpigmentation in the basal cell layer acanthosis and hyperkeratosis. A small amount of inflammation is present. Hypertrophy of the sebaceous glands has been noted.<sup>226</sup>

It is customary to distinguish between a benign and a malignant type of acanthosis nigricans. There is no difference in the morphology of the two types

<sup>222</sup>Mascorps, O. Keratosen, Acanthosis nigricans in Handb. d. H. u. G., 2, 31 373-403, 1931

<sup>223</sup>Kittner H. Die Acanthosis nigricans und ihre Bedeutung für die Diagnose des malignen Tumors, Zbl. d. Grenzgeb. d. Med. Chir. 35: 278-300, 1928

<sup>224</sup>Tennstedt, H. Ueber Acanthosis nigricans bzw. über einen Fall mit Beteiligung der Epiglottis, Virchow Arch f. path. Anal. 279: 253-261 1931

<sup>225</sup>Yamada, K. A Case of Acanthosis Nigricans, Jap. J. Dermat. & Syph. 25: 61 1935 224, 19

The adjective malignant refers to the association with malignancy not to a malignant course of the dermatosis itself. The benign type is also often called juvenile because many cases start in early childhood and remain stationary throughout later life. Some of these patients died later of cancer. Some of the juvenile cases were malignant and some adult cases at least clinically were not associated with malignancy.<sup>1836</sup> Thus there is no sharp borderline between the two types. The etiology and pathogenesis of acanthosis nigricans is far from being understood but there are some facts known which eventually may lead not only to the elucidation of the remarkable phenomena of this disease but also of other pigmentary disorders.



Fig. 329 — Acanthosis nigricans. Obesity. Juvenile case no malignancy. (Courtesy Division of Dermatology Department of Medicine University of Chicago.)

The most important etiologic fact is that at least 50 per cent of the cases of acanthosis nigricans occur in patients with cancer. Fully 92 per cent of these malignancies were found in the abdominal viscera mostly in the stomach. Almost all of the nonabdominal cancers had abdominal metastases.<sup>1837</sup> The course of many neoplasms associated with acanthosis nigricans is highly malignant.

<sup>1836</sup>Burgess, N. A Case of Acanthosis Nigricans, Brit. J. Dermat. 43: 169-177, 1951.

<sup>1837</sup>Odendoff, Curt H. Cancer Associated With Acanthosis Nigricans. Can. Arch. Surg. 47: 817-853, 1943.

In trying to explain the peculiar pigmentary skin disease which has some features of Addison's disease, the thought of an adrenal etiology has arisen. However, at least twelve cases are on record in which autopsy failed to show any adrenal involvement. H. O. Curth<sup>207</sup> who has recently reviewed the available material with regard to other endocrine glands, arrives at the conclusion that theoretic considerations and actual records of cases speak against endocrine

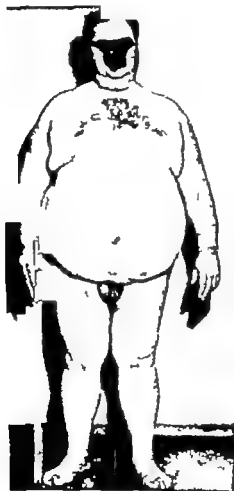


Fig. 840.—Obesity of pituitary type in patient with acanthosis nigricans. (Courtesy Division of Endocrinology, Department of Medicine, University of Chicago.)

disturbances as a causative factor in acanthosis nigricans. Yet a great number and variety of endocrine disorders have been found in association with acanthosis nigricans. It seems that although at the present time no satisfactory endocrinological etiology can be propounded, the described associations with obesity, debility, dwarfism, genital hypoplasia, diabetes, goster, cryptorchism, achondro-



plasia and acromegaly cannot be slighted. Puberty exerts a provoking influence on the onset or development.<sup>3037</sup> Of great interest is the case of Hellerström<sup>3038</sup> who observed marked though not complete regression of the diffuse papillomas after castration of a male patient. Ketosteroid determinations do not seem to have been done in acanthosis nigricans. In a few cases the dermatosis subsided after treatment of the cancer and recurred with it (Spieschka after Moncorpe<sup>3039</sup>). Spreading of acanthosis nigricans after stationary periods seems to coincide with the development of cancer.<sup>3037</sup> These observations point to the neoplasm itself as a cause. But the great rarity of acanthosis nigricans compared with the frequency of abdominal neoplasms compels one to believe that a rare combination of factors must be required. The same conclusion must be applied to the association with other diseases. The dermatosis usually preceded in some cases for many years the development or at least the discovery of cancer. The etiologic role of the abdominal *sympathetic* system is not yet clear. Stimulation of the chromaffin system could explain the hyperpigmentation but not the other aspects of the syndrome. Most cases have not been investigated thoroughly from this view point. In one case the resection of a cervical ganglion resulted in rapid regression of acanthosis nigricans in the axillary areas.<sup>3040</sup> Ten instances of *familial* occurrence, all of the benign type have been observed.<sup>3037</sup>

The *treatment* of acanthosis nigricans is at best symptomatic unless regression occurs after extirpation of the malignancy. The *prognosis* of juvenile acanthosis nigricans as a dermatosis is that of an incurable though in itself not dangerous, anomaly comparable to a widespread nevus. However the prognosis of the juvenile benign variety is darkened by the frequent association with systemic disease. The prognosis of the cases starting in the age group from 20 to 40 years is doubtful. Acanthosis nigricans which develops after the age of 40 is almost certain to be indicative of cancer usually visceral<sup>3041</sup> which when the dermadrome appears, already has metastasized. Exploratory laparotomy is inadvisable (O Leary in discussion to Michelson<sup>3042</sup>).

<sup>3037</sup>Hellerström, R. Zur Kenntnis der Acanthosis nigricans. Act. dermat. —venereol. 14: 86-93 1923. Skt. 46: 180 1971.

<sup>3038</sup>Jonsson, J. O. and Montgomery, H. Acanthosis Nigricans and Pelvic Malignancy. Proc. Staff Meet. M. ye. Clin. 13: 113-117 1935.

## CHAPTER XXXVI

### DISORDERS OF THE NERVOUS SYSTEM

The function of the skin as an organ of sense may become affected by disturbances of the peripheral sensory nerves as well as of the central nervous system. Cutaneous secretion, palomotion, vascular tonus, and trophic balance depend on the autonomic nervous system, the functioning of which may be disturbed by local organic lesions as well as by reflexes and hormonal activations originating somewhere else. These considerations give us an idea of the complex mechanisms by which a great variety of noxae, including malformations, injuries, infections, poisonings, and endocrine disorders, may produce dermadromes of neurogenic character.

#### Cutaneous Senses 1224, 1229, 1231

A variety of specialized nerve endings gives the skin the character of a sense organ. The perception of all cutaneous stimuli is not diffuse as it seems to be but localized in points which are distributed over the skin in varying density. The end organs related to the sensitive spots are highly specialized in their functions. Thus, forcing of a needle into a Meissnerian body does not cause pain but only the sensation of touch. The warmth spots are most dense on the face and on the lateral aspects of the fingers (2 per square centimeter). The cold spots are much more numerous with the greatest density on the face and on the trunk. About 11 cold spots can be mapped out on one square centimeter of facial skin.<sup>1224</sup> About one-third of the body surface is unable to perceive warmth.

Free nerve endings in the epithelium, radiating from subepithelial plexuses, receive the stimuli causing the sensation of pain. The skin has only one quality of pain but differences in intensity and duration may cause such varieties as burning, pricking, and soreness. Lewis and Heiss<sup>1229</sup> believe that pain is caused by a substance produced in the tissue and acting on the endings of the pain nerves. This hypothetical substance does not seem to be histamine.

The pain spots are most dense in the popliteal fossa with 232 per square centimeter and least dense on the tip of the nose with only 44 per square cm.<sup>1224</sup> The sense of touch is also localized in points which are mostly situated at the hair follicles. The nerve endings surround the follicles like a basket. The bent hair acts as a lever and intensifies the pressure on the end-organs. The hairs widen the perceptive area of the follicle and make the point system appear diffuse. A shaved area is considerably less sensitive to touch than a hairy one.<sup>1229</sup> The

<sup>1224</sup>Grünwald, E. *Haut und Nervensystem*, Handb. d. H. Ch. 6, 2 1222-1261 1923

<sup>1229</sup>Van Frey, M. and Reiss, H. *Physiologie der H. u. Haut* d. H. Ch. 2, 2 1929

<sup>1231</sup>Lewis, T. and Heiss, W. *Pain Derived From the Skin. Mechanism of Production*, *Neur. St.* 29-61 1923.

sensation caused by a constant stimulus for example the bending of a hair soon fades and is no longer perceived. This phenomenon is called adaptation. Because of adaptation we do not feel the weight of our clothes and a needle prick is painful only for a moment. The pain will stop in spite of the fact that the needle is still sticking in the skin. We do not feel a temperature which does not change.

**Nerve Section**—The effect of cutaneous nerve section was studied in famous self-experiments by Head. Foerster<sup>2622</sup> in evaluating nerve injuries caused by gun shots during and after the first World War and other authors<sup>2623</sup> modified Head's observations to some extent.<sup>2620</sup> The section of a sensory nerve immediately abolishes all forms of skin sensibility. The areas of thermal, tactile and analgetic anesthesia after section of the nerve are not entirely congruous. Section of the ulnar nerve for instance leaves a zone in part two inches in width in which only pain but not touch or temperature can be felt. The disturbance of the perception of temperature is more extensive than that of touch and pain and the loss of the perception of warmth is more extensive than that of cold.<sup>2624</sup> With the regeneration of the nerve the sensibility returns in two stages. The two stages are explained by some authors by the existence and the difference in the regeneration of two kinds of fibers.<sup>2625</sup> After seven to thirty weeks a markedly punctate sensibility appears with relatively wide anesthetic areas in between. However the perception of intensities and the localization of a punctate stimulus is inaccurate and radiating widely from the point of stimulation. The threshold for pain is high and the character of the pain is described as "sickly" meaning of an unusual quality. This quality is illustrated by the peculiar sensibility of the cornea and the glans penis which normally are of similar character. The author can from his own experience with a severed lingual nerve confirm the statement of Trotter and Davis (after O. Foerster<sup>2626</sup>) that the character of the pain is different from the normal sensation of pain. Only extremes of temperature are recognized in this stage. The temperatures between 24 and 38°C do not cause a sensation of heat. This first stage of the return of the sensibility is called protopathic sensibility.<sup>2628</sup> It is followed by the return of the sensation of light touch of tactile localization and discrimination as measured by the ability to recognize two compass tips as two distinct points, and finally by the restoration of normal sensibility. The second stage of recovery is referred to as epicritic sensibility. Complete restoration of the sensory functions may take up to two years. In skin grafts the sensibility returns after 1 to 12 months and progresses centripetally.

The section of a nerve abolishes the sensory functions in only part of the innervated area. Overlapping of neighboring innervations creates marginal hypoesthetic zones. A persistent circumscribed dermatitis may occasionally follow the section or injury of a nerve. These lesions are restricted to the area supplied.<sup>2627</sup> They have been used as evidence for a neurogenic theory of eczema.

<sup>2622</sup>Foerster, O. *Symptomenatologie der Schwerverletzungen der peripheren Nerven*, Berlin, 1929.  
<sup>2623</sup>Julius Spixberger.  
<sup>2624</sup>Langer, L. H., Garney, H. M. and Wilson, W. D. Cutaneous Innervation, *Arch. Neurol.* 24: 1-60, 1934.

<sup>2625</sup>Rothman, S. *Physiology of Itching*, *Physiol. Rev.* 21: 387-391, 1941.

<sup>2626</sup>Head, H. *Sensibilitätsstörungen*, Berlin, 1900.

<sup>2627</sup>Herrick, R. Dermatitis Following Nerve Injury, *Arch. Derm. & Syph.* 24: 879-881, 1923.

The sensibility of the skin is considerably influenced by the vegetative system. For example partial nerve section alone rarely causes circumscribed pruritus or hyperesthesia. This could, however be experimentally produced by simultaneous nerve section and sympathectomy<sup>303</sup> Vitiligo and canities have often been observed in the area supplied by peripherally diseased nerves frequently with neuralgia.<sup>120</sup> This is most often seen in neuralgia of the trigeminal nerve. Zosteriform pigmentations after nerve injury are also known. Paresthesias like numbness or formication give little information about the nature of the nervous lesion<sup>300</sup>

Nerve injury section and central destructive processes may cause *trophic ulcers*. The trophic, i.e. the nutritional balancing influence of the nervous system cannot be denied. The much disputed and not definitely answered question of specific trophic fibers does not seem to be important any longer since the trophic effects can be sufficiently explained by the known functions of the vegetative system.<sup>305</sup> Trophic ulcers are mostly seen on the pressure points of the feet and other sites subject to trauma or infection e.g. hands nasal septum and the mouth<sup>304</sup> The perforating ulcer has been observed in a great variety of organic lesions e.g. peripheral nerve injury or therapeutic dissection<sup>306</sup> postencephalitic states, tabes, syringomyelia, cervical rib<sup>307</sup> and others. The ulcer starts as a blister or a sinus underneath a callus. Keratosis of the edge and absence of granulations in the floor are characteristics of the fully developed lesion. The size and course are variable. Keratosis and sinus formation may be excessive causing deep destruction of bones.

*Itching Superficial and Deep Tickling* The dermatologically most important neurocutaneous symptom is pruritus. Itching can be elicited by vibrating or constant, subthreshold tactile stimulation i.e. tickling<sup>308,309,310</sup> If the stimulus exceeds a certain threshold the normal sensation of pain or touch results, and replaces the itching sensation. Scratching relieves itching by replacing it with pain to which itching has many relations.<sup>308</sup> Anesthetic areas as a rule do not itch. Intact perception of touch and pain is usually<sup>309</sup> but not necessarily a prerequisite for the eliciting of itching by superficial tickling i.e. light stroking with a hair or wisp of wool. Thus itching or superficial tickling may still be felt if a hair is lightly run over an analgetic zone in a tabetic, when a needle prick fails to cause pain. In peripheral neuritis, tickle is increased where there is intensification to all forms of adequate painful stimuli. In syringomyelia, a loss of pain and tickle seem to coincide. With lesions in the *optic thalamus* there is often intensification of the response to tickling stimuli over the same side of the body on which the responses to painful stimuli are exaggerated. With lesions of the internal capsule and cerebral cortex which have resulted in impairment of sensibility

<sup>303</sup>Aubrey, E. A.: Action seculaire et action du sympathique dans l' prurit par lésion sensitive partielle. *Compt rend Soc de biol* 111: 81-92, 1912

<sup>304</sup>Toussaint, L.: Siècles neuro-vasculaires cutés. *Oltr Mal di dermat.* 41: 75 372-423 1924.

<sup>305</sup>Darier, J.: Lésions trophiques de la bouche et des fosses nasales (mal perforant buccomaxillaire des tabétiques) et le problème des nerfs trophiques. *Ann. de Dermat.* 8: 97 126, 1917

<sup>306</sup>Wickman, F.: Cervical Rib (in skin diseases). *Arch. Dermat. & Syph.* 55: 716, 1937

<sup>307</sup>Ortchard, E. A. B.: The Clinical Significance of Variations in Tickle Sensibility. *Proc Roy Soc.* 112: 261 297 704, 1933

neither tickle nor pain sensibility is impaired both are occasionally overactive.<sup>300</sup> This is explained by the assumption that the tickle sensation is conducted by the peripheral neurons to the cord where the pathways cross to the other side in the posterior commissure run through the cord and the medulla near the spinothalamic tract and are finally registered in the optic thalamus not in the cortex.<sup>301</sup> Therefore cortical depressants like morphine paraldehyde and bromine do not influence itching as much as thalamic drugs like phenobarbital.<sup>302</sup> Section of the anterolateral tract of the spinal cord abolishes tickling and itching at the corresponding level while section of the posterior tracts exaggerates these sensations and protopathic pain to which itching is intimately related.<sup>303</sup>

Drugs which paralyze the sympathetic system like ergotamine tartrate or stimulate the parasympathetic system like yohimbine and muscarine seem to inhibit itching. Königstein<sup>304</sup> concludes from these observations that the sympathetic system plays a part in the genesis of pruritus. Pruritus seems to be closely connected with dilation of the smaller vessels. It is perhaps a response to changes in the state of permeability.<sup>305</sup> The psychogenic influence is powerful. This also underlines the importance of the sympathetic factors. Scratching as a prompt reflex reaction to itching is not fully developed before the age of one year<sup>306</sup> but general reactions may be seen as early as the sixth hour of life. Deep tickling is entirely different from superficial tickling and itching though the same word is often used indiscriminately. One should speak of deep tickling when the sensation is felt in deeper structures and when a considerable pressure is necessary to elicit it. Von Frey<sup>307</sup> relates deep tickling to the sense of pressure superficial tickling to the sense of pain. Tickling is mainly though not exclusively confined to certain areas like the anterior aspect of the neck, the armpits the abdomen and the clitoris. A sensation more similar to deep tickling than to itching occurs in the mucosae too e.g. rectum urethra larynx and trachea. A characteristic of deep tickling compared with itching is its relation to uncontrolled reflexes like laughter and other widespread muscular contractions. The cringe reflex of tickling is well known.<sup>308,309</sup> Tickling does not elicit scratching but muscular defense.

Head's hyperalgesic zones are due to the projection of visceral pain to certain segmental skin regions. These regions correspond to those observed in herpes zoster. Head<sup>310</sup> mapped such skin zones for many internal organs (see M. Lewandowsky<sup>311</sup>). The validity of the phenomenon has been amply confirmed though there are many controversies over details. It should be emphasized that

<sup>300</sup>Hyman and H. and Königstein H. Klinische und experimentelle Untersuchungen über das Juckreizphänomen. Wiener klin. Wochenschr. 43: 307 1930, 1931 II.

<sup>301</sup>Königstein H. Zur Entstehung und Bekämpfung des Juckreizes. Wien klin. Wochenschr. 43: 326.

<sup>302</sup>Hirsch W. Die Bedeutung des vegetativen Systems für die Entstehung des Juckreizes. Dermatolog. Klin. (Graz) 1: 129 1935 2b: 453.

<sup>303</sup>Hartmann-Harphiz D. Juckempfindung. Krassen Phosphorvergiftung im Säuglingsalter. Jahrb. f. Kinderk. 153: 140 31.

<sup>304</sup>Von Frey M. Über den Kitzel. Starch H. Arch. Fortbild. 33: 81-83 1935.

<sup>305</sup>Dreher H. G. Emotions and Bodily Changes. New York, 1935. Columbia University Press.

<sup>306</sup>Debar H. F. Physical and Mental Relationship in Infancy. Am. J. Psychiat. 61: 41-463, 1934.

<sup>307</sup>Lewandowsky M. Die zentralen Sensibilitätsstörungen, Handb. d. Neurologie, Berlin, 1910. Julius Springer.

Head & zones are hyperalgesias. The sensibility to touch is not increased. The diagnosis of Head & zones is made by needle pricks or by slight pinching. Alterations of the sensation caused by tickling with a blunt object have been found to correspond with Head & zones. These zones of decreased rarely increased sensitivity to tickling are supposed to occur more frequently than the hyperalgetic zones. They indicate the same organ relationship.<sup>200</sup> A vasomotor reaction to a weak galvanic stimulus can also be used.<sup>201</sup>

*Herpes zoster* of the corresponding region may though rarely be the only manifestation of a visceral disease e.g. peptic ulcer gallstones or cardiac disease.<sup>202</sup> It is assumed that the viscerocutaneous relation which consists of viscus—sympathicus—intervertebral ganglion—ramus visceralis—gray matter of the spinal cord—anterior root—spinal nerve—skin is affected in the intervertebral ganglion which probably becomes the site of the herpes zoster infection. An interesting visualization of the cutaneous zone corresponding to a lung focus was observed after a weak ultraviolet radiation. Only the skin corresponding to the tuberculosis lung focus showed an erythema.<sup>203</sup> Circumscribed edema in the viscerocutaneous zones has also been observed.<sup>204</sup>

<sup>200</sup>Krieger, H. Veränderungen des Schmerzgeföhls der Haut bei Organerkrankungen, Würzburger Abhandlungen, vol. 23, No. 5, Leipzig, 1930, Carl Kabitsch.

<sup>201</sup>Kahane, M.: Die cutane Diagnostik innerer Krankheiten, Wien. Arch. f. inn. Med. 3: 67-110, 1921.

<sup>202</sup>Arnstein, A. Herpes zoster als scharfes manifestes Symptom von im übrigen latent verlaufenden Erkrankungen innerer Organe, Wien. klin. Wochenschr. 34: 13-14, 1921.

## CHAPTER XXXVII

### DISORDERS OF THE NERVOUS SYSTEM

#### The Autonomic Nervous System

The autonomic or involuntary nervous system innervates the sweat glands the muscoli arrectores pilorum and the tonus of the blood vessels probably also the secretion of the sebaceous glands. Almost every cell of the skin is surrounded by an extremely fine reticulum of sympathetic fibrils, the so-called sympathetic basal plexus or terminal reticulum (Stöhr after F. John<sup>300</sup>).

**Sweating**—The innervation of perspiration has a subcortical center in the hypothalamus. From there the sudomotor impulses descend through the brain stem the medulla and a series of spinal centers, to the anterior roots and the peripheral sympathetic pathways (Walker after Rothman<sup>301</sup>). A major crossing takes place in the lower pons.<sup>302, 303</sup> The pathway of the sweat inhibiting action runs through the posterior roots.<sup>302</sup> In spite of their sympathetic pathway the sudomotor fibers behave like parasympathetic or cholinergic nerves. Their stimulation causes liberation of acetylcholine in the skin and therefore can be suppressed by atropine and enhanced by physostigmine. The formation of acetylcholine in the venous return of a perfused cat leg has been demonstrated with the esterized leech preparation.<sup>304</sup>

Sympathectomy and the section of a peripheral nerve (e.g. the sciatic) causes anhidrosis in the area supplied and hyperhidrosis in the surrounding margin.<sup>305, 306</sup> A reflexive hyperhidrosis can be observed in the corresponding symmetric zone.<sup>307</sup> Sweating tests are used in the diagnosis of postural hypotension and in determining the degree of completeness of sympathetic denervation after sympathectomy and removal of sympathetic ganglions.<sup>308</sup>

<sup>300</sup>John, F. Skin as Organ Controlled by Vegetative Nervous System, *Med. Welt* 13: 915-922, 1939.

<sup>301</sup>Rothman, S. Role of Autonomic Nervous System I. Skin Diseases, *Psychosom. Med.* 7: 90-96, 1945.

<sup>302</sup>Peet, M. M. and List, O. F. Changes of Sweating: Lesions of Pons, Medulla Oblongata, and Upper Cervical Cord, *Tr. Am. Neurol. A.* 68: 92-96, 1928.

<sup>303</sup>List, O. F. and Peet, M. M. Sweat Secretion in Man: Sweating Response in Normal Persons, *Arch. Neurol. & Psychiat.* 39: 1228-1237, 1935.

<sup>304</sup>Dale, H. H. and Feldberg W. Chemical Transmission of Secretory Impulses to Sweat Glands of Cat, *J. Physiol.* 82: 131-178, 1932.

<sup>305</sup>Frölich, A. and Sak, E. Untersuchungen über die periphere Schweißsekretion Kanarienvogel, *Schmidberg's Arch.* 168: 620-637, 1932.

<sup>306</sup>Ackermann, A. Studien zur Physiologie der Schweißdrüsen, *Dermatologica* 79: 219-224, 1939.

<sup>307</sup>Gut, KAREL, L. Motorische und vegetative Grenznenneffekte bei Läsionen peripherer und zentraler Abschnitte des Nervensystems, *Z. Neurol.* 147: 291-307, 1932.

<sup>308</sup>Brown, O. F. Clinical Tests of Function of the Autonomic Nervous System, *J. A.M.A.* 106: 352-357, 1932.

The spinal centers of perspiration and piloerection have been mapped and tabulated by Ottfried Foerster<sup>300</sup> Central cerebral lesions may cause contralateral hyperhidrosis (hémiplegie sudorale Binger and Berg after Marchi onini<sup>301, 302</sup> This however is only marked in early lesions since compensatory mechanisms soon develop and some fibers remain uncrossed Unilateral mostly facial hyperhidrosis is seen in connection with peripheral sympathetic disturbances, mostly injuries of the parotid area,<sup>303</sup> or after thyroidectomy<sup>304</sup> Unilateral sweating is often combined with flushing facial paralysis and disturbances of the parotid gland

Ackermann<sup>305</sup> found sweat secretion to be the resultant of two antagonistic processes In the proximal section of the gland sweat is secreted through parasympathetic impulses In the more distal part of the tubule a regulating reabsorption under parasympathetic and sympathetic influences may take place<sup>306</sup>

Our knowledge of the autonomic innervation of the *sebaceous glands* is meager A well known fact is the seborrhea which sometimes follows brain lesions especially of the midbrain and pons (see section on encephalitis)

The psychogalvanic reflex, or the Tarchanoff Veraguth phenomenon is the decrease in the *electric resistance of the skin* caused by sensory stimuli and psychic excitement The electric resistance depends on the amount of sweat and is one of the most sensitive psychosomatic reactions Any psychic concentration emotion or effort measurably increases the perspiration The lie detectors are based in part on the increased sweat secretion under emotion Food ingestion lowers the electric resistance

The reflex may become conditioned so that it occurs at meal time, even if no food is being eaten<sup>307</sup>

The electric resistance is high in areas which do not sweat Therefore the measuring of the electric skin resistance can be used for mapping the sudomotor innervation The areas affected by sympathectomy offer a high resistance to the passage of a very small direct current There may be variations, from a few hundred to many thousand ohms, within less than  $\frac{1}{4}$  inch The electric skin resistance is normally lowest in a sharply demarcated area which includes both eyelids, the nose, the mouth varying portions of the forehead of the cheeks, and of the skin under the lower lip During sleep this area becomes narrowed finally consisting of only a small margin around the mouth Similar areas of low resistance exist on the palms and the soles The patterns of areas of low

<sup>300</sup>Marchlesini A Hautkrankheiten und Nervensystem, Fortschr d Neurol, Psychiat. 6 7-23 1934

<sup>301</sup>Marchlesini A Hautveränderungen bei nichttypischen organischen Erkrankungen des Zentralnervensystems, Fortschr d Neurol Psychiat. 6 303-312, 1934

<sup>302</sup>Roger H Les cydreeses sympathiques d'hyperhidration faciale Riv clin med 34 161 192 1923

<sup>303</sup>Loeblin Vasomotorische und trophische Störungen nach Läsion des Hauptsympathicus, Klin. Monatschr f Augenb 87 524-536, 1931

<sup>304</sup>Wilson, W O Observations Relating the Innervation of the Sweat Glands of the Face Ctn. Sc. 2 173-216, 1926

<sup>305</sup>Reizberger H Das Elektrodermatogramm und die Nahrungsreflexe des Menschen, Krypt. d. Inn. Med u. Kinderh. 49: 122-165, 1923.



temperatures greater than  $3^{\circ}\text{C}$  justifies immediate amputation of a limb. The level of amputation should not show a temperature lower than  $1^{\circ}\text{C}$  below the corresponding level of the other side<sup>3673</sup> In diabetic gangrene the temperature may be raised therefore the skin temperature alone is not a reliable indicator for determination of the level of amputation<sup>3673</sup> In arteritis obliterans the feet may be warm In acute phlebitis the foot temperature is high The patient should stay in bed until the return of normal temperature.<sup>3673</sup> Inflammatory processes increase the skin temperature in a much wider area than the immediate neighborhood of the lesion itself This seems to indicate that not so much the increased local metabolism but rather the reflex arterial dilation is the cause of the heat in an inflamed area.

There is a rough parallelism between surface temperature especially of the foot and the basal metabolism so that under certain conditions the skin temperature may be used as a substitute or check for the usual basal metabolism test<sup>3673</sup> High foot temperatures are therefore not only found in hyperthyroidism but also at the end of pregnancy when the basal metabolism is usually increased These high foot temperatures persist during lactation In general anesthesia the rise of the foot temperature indicates that the patient is asleep Primary or secondary sinking of the foot temperature indicates impending or existing shock.<sup>3644</sup>

**Morphine Wheel**—If the skin is punctured with a needle through a drop of morphine solution a wheel and a surrounding flare appear Absence of the wheel indicates a block of the small arteries which feed the area as encountered in Buerger's disease If the peripheral nerve is degenerated the flare may fail to appear<sup>364</sup>

### Raynaud's Disease

An invariable association of the peripheral vascular spasms called Raynaud's<sup>3643</sup> disease with an internal disorder which might cause the nervous impulses leading to the attack has not been discovered In fact some analysts<sup>3643, 3664</sup> consider the absence of such a relation as a valuable criterion for the diagnosis of true Raynaud's disease However the abnormal sympathetic factor which leads to the circulatory changes cannot be denied Many modern writers on the subject deplore the rather careless labeling of a variety of vascular conditions as Raynaud's disease Raynaud himself being among the accused<sup>3672, 363</sup> Hunt<sup>363</sup> in an effort to clarify the situation defines Raynaud's phenomenon<sup>3636</sup> as intermittent pallor or cyanosis of the extremities, precipitated by exposure to cold without clinical evidence of blockage of the large peripheral vessels, and without or not more than skin deep nutritional lesions. However

<sup>3663</sup>Dickson, W The Temperature of the Skin Surface J A M A 106 1188-1192 1932.

<sup>3664</sup>Marthasoon, H Morphine Puncture A Method for Diagnosing Affections in the Peripheral Arteries and Nerves, *Acta dermat. venerol* 30: 508-512 1930.

<sup>3665</sup>Raynaud, A M M De l'asphyxie locale et de la gangrène symétrique des extrémités, Thèse de Paris, 1832.

<sup>3666</sup>Allen, E V and Brown, G E Raynaud Disease (147 Cases) J A M A 89: 1472-1478 1922.

<sup>3667</sup>Allen, E V and Brown, G E Raynaud Disease Diagnosis, *Am. J. M. Sc.* 123 187-200, 1922.

<sup>3668</sup>Hunt, J B. Raynaud Phenomena, *Quart. J. Med. S* 299-444 1930

<sup>3669</sup>Lewis, Th and Pickering G W Raynaud Disease *Heart* 1: 237-306 1924.

the time honored term Raynaud's disease defies eradication. If one keeps Hunt's definition in mind there is no reason to abolish it since the term disease is often used for a syndrome or phenomenon of unknown cause.

In the attack, the skin of the fingers, less often and less severe that of the toes, becomes suddenly pale and cool often painful. The skin temperature may be lowered as much as 16.7 centigrades (30 fahrenheit degrees). The volume of the involved part is decreased. In this stage a needle prick does not cause bleeding. Cyanosis (local asphyxia) predominates in severer cases and may produce a blue brown slate or even black color. The skin becomes white on pressure but is extremely slow in taking on the color of the surrounding area after the pressure has been released. The radial pulse remains perceptible during the attack. The attack ends with a change of the color to vivid red caused by a violent reactive hyperemia. The changes are symmetrical. The sensibility is often disturbed but not abolished and the disturbances of sensitivity are, like the pain ill-defined and not limited to the area supplied by one nerve. Anhidrosis or hyperhidrosis occurs. Only in severe cases do trophic lesions like shallow ulcers, paronychia, and atrophy of the nails muscles and bones become apparent. In later stages the finger tips may be covered with a great number of small depressed scars. If gangrene occurs, it is usually superficial and always dry. Hardly ever do areas larger than an end-phalanx become necrotic.

The attack can be precipitated in many cases by immersion of the hand in cold water or by exposure to cool air or by chilling of the body by cold drinks.<sup>367</sup> Cold is the most important immediate cause although emotion also plays an important part in the precipitation of the attacks.<sup>376,382,399</sup> The trouble is predominantly found in young and middle-aged women. The prognosis is usually good with respect to life, but the attacks may recur over many years. The pathogenesis of the phenomenon is still controversial. Raynaud and many others after him believed that an abnormal vasomotor tone was the main pathogenetic factor. Lewis (see Hunt<sup>380</sup>) produced much physiological evidence to the effect that the vasomotor tone was in order but that there was a local fault in the medium-sized digital arteries.<sup>380</sup> Several autopsies, on cases having had the disease for long periods of time, have not revealed any changes in the arteries,<sup>384,392</sup> but a few instances of endarteritic alterations have been observed (Kolisch after Mucha<sup>386</sup>). Microscopic changes in the sympathetic ganglia and other nervous centers are on record.<sup>380</sup> The vascular as well as the neural findings are not uniform and some are probably secondary. The capillaroscopic picture during the attack is characterized by the empty and seemingly absent

<sup>367</sup>Johnson C. A. Raynaud Disease, *23 Obst. Surg. Gynec. & Obst.* 72: 589-607, 1941.

<sup>368</sup>Craig J. B. Raynaud's Disease Psychogenesis, *Dis Nerv. System* 8: 143-145, 1944.

<sup>369</sup>Mahon J. Raynaud's Disease, *Ann. Int. Med.* 30: 228-232, 1944.

<sup>370</sup>Hjelmman O. K. and Wallin, J. Raynaud Disease Vascular—not Sympathetic—Disease, *Am. Heart J.* 22: 535-554, 1942.

<sup>371</sup>Dannigert H. Ein Fall von Raynaud'scher Krankheit mit Obduktionsbefund, *Das Freiburg J. B.* 1922.

<sup>372</sup>Leviche, R. and Fantaleo, R. Sur la nature de la maladie de Raynaud, *Presse med.* 1922 II 1921-1925.

<sup>373</sup>Merkz, V. Die Raynaud'sche Krankheit, *Handb. f. H. u. Gk.* 6, 2: 272-300, 1922.

<sup>374</sup>Palmer Doehrmann J. and Armand. Lésions de la chaîne sympathique dans la maladie de Raynaud, *Lyon med.* 1921 II 117-124. *Idem.* 49: 71.

capillaries and the constricted arteries. The spastic picture is followed by atonic dilatation in the asphyctic stage but both spasm and atonia may be seen simultaneously.<sup>10</sup> The capillarscopic changes exceed the macroscopically changed areas. There can be no doubt that vasomotor stimuli play an important part. This is best demonstrated by the immediate success of surgical removal of the sympathetic fibers or ganglia through which the vasomotor stimuli must pass. After sufficiently extensive sympathectomy by one of the many suggested methods (Review and Methods see Homans<sup>11</sup> and Adson<sup>12</sup>) the vascular paralysis which follows the operation leaves the fingers flushed and no attacks occur as long as the sympathetic fibers do not regenerate.

The associated conditions which can be found in patients with Raynaud's disease are most often of functional character. In 24 per cent of a series of 147 noncomplicated cases psychoneurosis or neurasthenia was obviously a feature.<sup>13</sup> Syphila arteriosclerosis and a number of rare diseases<sup>14</sup> have been found in connection with Raynaud's syndrome. Limenthal<sup>15</sup> described 3 cases with pulmonary fibrosis. A rare finding is a cervical rib. If this anomaly is unilateral the attacks are unilateral but intermittent in spite of the continuous cause.<sup>16, 17, 18, 19</sup> Menopause<sup>20, 21, 22</sup> sclerodactyl, <sup>23, 24</sup> arsenical <sup>25</sup> and copper poisoning<sup>26</sup> are other rare combinations. Lewis and Landis<sup>27</sup> make use of the combination with sclerodactyl to support the arteritic theory of Raynaud's disease. Scler<sup>28</sup> separates sclerodactyl (acroscclerosis) from Raynaud's disease as well as from scleroderma. Combination with tetany<sup>29</sup> and calcifications<sup>30, 31</sup> have caused speculation about a parathyroid etiology. Subtotal parathyroidectomy has not proved successful.<sup>32</sup>

*Treatment*.—Since the paralytic hyperemia does not last the enthusiasm about the surgical approach has somewhat abated so that lately medical management has again been said to give equally satisfactory results. Johnson<sup>33</sup> stresses prevention of attacks by avoiding the thing that precipitates them.

- <sup>10</sup>Adson, A. W. Raynaud Disease. Results of Sympathectomy, B. Ohio North America 17 1081-108 1937.  
<sup>11</sup>Limenthal H. Raynaud Disease. Pulmonary Fibrosis 3 Cases, New England J. Med. 227: 432-436, 1943.  
<sup>12</sup>Méjean, J. and Lefevre M. Côte cervicale bilatérale. Syndrome de Raynaud unilateral, Bull. et mém. Soc. nat. de chir. 61 1073-1083, 1923. Ed. 59: 463.  
<sup>13</sup>Amir, H. Vasomotorisch-trophische Neurosen, ed. 2, Berlin, 1923, S. Karger.  
<sup>14</sup>Werber Raynaud'sche Krankheit und Urticaria chronica papulosa, Zbl. 14 59, 1924.  
<sup>15</sup>Forero A. Raynaud Disease in Menopause. Wien. med. Wchnschr. 78: 2370-2371 1933.  
<sup>16</sup>Berger Gefäßkrankung der Hände im Klimakterium. Zbl. 40: 577 1923.  
<sup>17</sup>Berger B. O. and Poppel, M. H. Raynaud's Disease, I. Unilateral Calcinoses Circumscripta. Assoc. of With Scleroderma. Radiology 29 80-88 1943.  
<sup>18</sup>Winn, A. Ueber Kapferch-Edgersons und die Beziehung zum Raynaudischen Symptomenkomplex, Arch. f. Dermatopath. 3 71-80, 1931. Ed. 28 406.  
<sup>19</sup>Lewis T. and Landis E. M. Raynaud Disease, Special Reference to Arteriole Defects and Scleroderma. Heart 18 320-330, 1931.  
<sup>20</sup>Bedel, J. Akrochroose und Raynaud'sche Krankheit, Arch. f. Dermat. u. Syph. 178 252-256, 1930.  
<sup>21</sup>Berowsky M. L. Die Pathogenese der Raynaud'schen Krankheit, Deutsche Zeitschr. f. Nervenk. 114 223-234, 1930.  
<sup>22</sup>Rhee, G. von Raynaud Disease With Calcareous Deposits, Arch. Dermat. & Syph. 29 520, 1934.  
<sup>23</sup>Walker E. H. Calcification in Raynaud's Disease, Proc. Roy. Soc. Med. 27: 827-833, 1934.

Secondary anemia should be treated. Pancreatic extracts and thyroid<sup>774</sup> have been advocated. Paraffin baths also have given considerable relief. The attack is best treated by immersion of the hands into warm not hot water.

**Erythromelalgia (Wel Mitchell's Disease)**—This syndrome features attacks of severe pain, redness and swelling usually of the feet. Hyperhidrosis is usually present in the involved area. The paroxysms are sometimes precipitated by exposure to warmth and depression of the limb. Though occasionally associated with Raynaud's disease it exhibits in many respects the opposite phenomena. Among a great number of occasional associations the connections with polycythemia (see there), Bence-Jones albuminuria and neurasthenia must be mentioned.<sup>760, 762, 770, 772</sup>

### Acrodynia (Feer's Disease; Pink Disease)

Acrodynia though probably known and described in France under this name<sup>773, 775</sup> more than a century ago has become better understood and more sharply defined only during the present century. The names of Swift<sup>774</sup> Selter<sup>776</sup> and particularly Feer<sup>771</sup> after whom the disease is often named designate some of the many authors who have been concerned with it.

The disease affects small children almost exclusively. According to Feer<sup>771</sup> the onset is insidious. The children are listless irritable sometimes vicious and do not care to play. The facial expression is frowning unchildlike weary so that the experienced physician can make the diagnosis on the physiognomy alone "especially if the contracted eyelids are added to the picture. The sleep is disturbed and the appetite lost. Fatigue and gradually developing motor disturbances like unwillingness or inability to walk or stand a bizarre and persistent jackknife-like position in bed with the head between the feet general flaccidity of the muscles without atrophy frequent light tremor and other nervous symptoms, are essential features. Other important signs are increased pulse rate and blood pressure high basal metabolism high blood sugar and high sedimentation rate. The temperature may be normal but fever has often been observed in the beginning and during complications. Monothermia is sometimes a remarkable feature. Encephalitic features resembling parkinsonism have been observed.<sup>771</sup>

<sup>770</sup>Tigges, J. Berl. Fälle von der Raynaudischen Krankheit mit C. Verengungen der Arterien, *Act. chir. Acad.* 71: 82-89, 1902. *Id.* 48: 474.

<sup>771</sup>Hirschfeld, R. Die Erythromelalgie, *Handb. d. H. Gk.* 6, 200-372, 1922.

<sup>772</sup>Levin, Th. Clinical Observations and Experiments Relating Burning Pain in the Extremities and to so-called Erythromelalgia, *Clin. Sc.* 2: 178-211, 1932.

<sup>773</sup>Dreus, G. E. Erythromelalgia and Other Disturbances of the Extremities Accompanied by Vasodilatation and Burning, *Ann. J. M. Sc.* 63: 469-488, 1932.

<sup>774</sup>Charcot, De l'acrodynie ou épidémie qui régnait à Paris depuis 1826, *Rev. méd. franc. et étrang.* 8: 81, 1830.

<sup>775</sup>Péan, M. Acrodynie d'antrefois et acrod. d'aujourd'hui, *Bull. Acad. de méd. Paris* 111.

111: 847-852, 1934.

<sup>776</sup>Swift, H. Erythroedema, *Lancet* 1: 811-81 (Letter to the editor).

<sup>777</sup>Selter, F. Acrodynia, 48 Cases, *Arch. f. Kinderh.* 80: 244-252, 1927.

<sup>778</sup>Feer, E. Acrodynia in Petermann. Translations of Pfaundler and Schlesmann in *Diseases of Children*, Vol. III Philadelphia, 1928. J. B. Lippincott Co. pp. 483-444.

<sup>779</sup>Morquio, L. Ueber einen Fall von Infantiler Akrodynie, *Arch. d. pediat. d. Uruguay* 3: 105-118, 1922. *Id.* 43: 48.

Acrodynia takes a protracted course over many months. Complete recovery is the rule. Recurrences are rare.<sup>3719</sup> The mortality rate among 200 cases in Australia was 3 per cent <sup>3720</sup> when the patients were treated in their own homes but rose to 30 per cent under hospital care with the danger of intercurrent infection. Higher mortality rates have also been observed <sup>3717,3721-3722</sup>

**Dermadromes**—Dermadromes occur frequently <sup>3723</sup> and may at times completely dominate the picture. From the start the skin feels cold clammy and flabby. Sweating to a degree which has its equal only in miliary fever weakens the patient and causes thirst. Sparse or copious millaria rubra<sup>3724</sup> or micro-papular follicular eruptions, soon follow the excessive sweating. The skin between the miliary papules may be diffusely bluish or red the feature from which the



Fig 341—Acrodynia. Freeling (Patient of Dr. A. E. Kohn)

name pink disease was derived (Glubbe after Crawford<sup>3725</sup>). The papules may enlarge and become scaly and eczema-like. Cases of acrodynia have often been mistaken for eczema as long as the other important symptoms had been overlooked. In typical cases of acrodynia the macerated skin soon peels in large

<sup>3719</sup>Pébus, M. Recidivations of Infantile Acrodynia, *Sch. elz. med. Wchnsch.* 71: 1307-1308 1941.

<sup>3720</sup>Wood, A. J. and Wood, J. Pink Disease, *Brit. M. J.* 5803: 537-531 1932.

<sup>3721</sup>Ratcliffe, T. A. Acrodynia, *J. Ment. Sc.* 87: 548-571 1941.

<sup>3722</sup>Bede, H. S. Die Feersche Krankheit im Licht der Dermatologie, *Arch. f. Dermat. u. Syph.* 187: 18-45, 1933.

<sup>3723</sup>Foerster, H. R. Erythredema Polysomiticum, *Arch. Dermat. & Syph.* 12: 17-23 1923.

<sup>3724</sup>Crawford, S. Juvenile Acrodynia, Eleven Cases, *Arch. Dermat. & Syph.* 28: 218-227 1922.

<sup>3725</sup>Anderson, H. and Bateman, L. 18 Cases of Acrodynia, *Rev. méd. de la Suisse Rom.* 90: 783-794 1920.

<sup>3726</sup>Foerster, A. Hautveränderungen bei der Feerschen kindlichen vegetativen Neurose (Säfer'sch. Feersche Krankheit), *Arch. f. Dermat. u. Syph.* 172: 282-290 1932.

flakes or in smaller circular patches. The *peeling* is particularly marked on the hands and feet so that it may be mistaken for scarlatina. Besides rashes from sweating and repeated crops of macular urticarial or multiform exanthema may occur especially on the mesial areas of the trunk,<sup>2772</sup> sometimes also on the extremities. Itching is most violent. Scratching and possibly trophic disturbances may cause pyodermic, ulcerative and necrotic complications. Bed sores occur quite frequently. The teeth may become loose and fall out. Geographic tongue is a frequent feature.<sup>2773</sup> Salivation frequently adds to the discomfort and may outlast the excessive perspiration. The hands and feet show a characteristic purplish pink erythema. The nose and cheeks may also be red.

The *hair* becomes dull and is often shed. The young patients often like to pull the loose hair out and the vertex frequently becomes bald.

Diffuse and focal inflammatory changes have been found in the sympathetic system so that the disease has been explained as a disorder of the vegetative nervous system and the term *parasympathitis* used.<sup>2774,2775-2778</sup>

The nature of the anatomical changes in the cerebrospinal system are still controversial.<sup>2779-2784</sup> Several neurologists believe that encephalitis influencing the vegetative centers of the *thalamencephalon* plays a part. In the skin hyperkeratosis parakeratosis, intracellular edema<sup>2785</sup> and inflammatory infiltrations in the stratum subpapillare with damage or loss of the elastic fibers and vasodilatation are microscopic features. Bode<sup>2786</sup> described eosinophile bodies in the prickle cell layer surrounded by lamellated cells.

The disease is probably an infection of the autonomic nervous system though neither microbes nor positive animal inoculations have been demonstrated. However local accumulations of cases, a few familial cases,<sup>2779,2787</sup> the seasonal increase in winter and spring and the existence of fever inflammation and apparent but not invariable immunity after recovery make the infectious etiology attractive. Endocrine<sup>2788</sup> toxic avitaminotic or chronic neurotrophic<sup>2789</sup> hypotheses have been suggested. An interesting argument in favor of the in-

<sup>2772</sup>Péris, M. Dechaume, J. and Bouchement, J. L'acrodynie infantile. Anatomie pathologique, Bull. Acad. de méd. Paris III a 113 812-823 1938.

<sup>2773</sup>Péris, M. and Bouchement, J. L'acrodynie infantile. Att. 15 Congr. Ital. Pédiat. pp. 867-868, 1934. Ebl. 52: 222.

<sup>2774</sup>Péris, M. Dechaume, J. and Bouchement, J. Sur l'acrodynie infantile, Rev. franç. de pédiat. 23: 226-276 277-310, 526-607 1936. Ebl. 54: 332.

<sup>2775</sup>Le Corquand, O. Dechaume, J. and Sedallian, P. Tentatives d'expérimentation sur l'acrodynie exophyllite spontané du lapin. Ann. de méd. 61: 88-99 1937.

<sup>2776</sup>Chémeret, R. Formes typiques de l'acrodynie, Presse méd. II 1607 1610 1935.

<sup>2777</sup>Wolf, I. J. and Davison, Ch. Acrodynie, J. Pediat. 4: 498-506, 1934.

<sup>2778</sup>Deauser, W. C. and Bakland, O. R. Acrodynie, Am. J. Dis. Child. 48 1228-1232, 1934.

<sup>2779</sup>Beccocq, O. P. and Meyer, R. Étude Clinique et Anatomopathologique d'une forme grave d'acrodynie, Rev. franç. de pédiat. 8 495-503, 1932.

<sup>2780</sup>Beckmann, G. Mouton, H. and Lecomte, A. L'acrodynie, maladie contagieuse? Présentation de deux frères acrodyniques, Bull. Soc. de pédiat. de Paris 21 124-127 1923.

<sup>2781</sup>Beckmann, G. and Lecomte, A. Acrodynie familiale (Trois enfants). Bull. Soc. de pédiat. de Paris 22 429-432 1928.

<sup>2782</sup>Kietzsch, H. Zur Pathogenese der Feerschen Krankheit, Deutsche med. Wchnschr. 1932, I 723-725.

<sup>2783</sup>Bode, H. G. and Schreuffer, A. Feersche Krankheit. Ebl. 63: 381-383, 1923-1923.

fectious etiology is the epidemiological and clinical relationship to acute miliary fever which has similar geographic distribution and symptomatology. Its course however is much more acute and dangerous.

No specific treatment has been found. Feer advocates high doses (2 mg daily) of atropine. Ultraviolet light has also been found effective.

## CHAPTER XXVIII

### DISORDERS OF THE NERVOUS SYSTEM

#### Neurocutaneous Diseases

The common ectodermal origin of essential parts of the skin and the nervous system is reflected in some diseases which affect both systems at the same time and in the same or at least in a comparable manner. These diseases have been called neurocutaneous diseases or congenital ectodermoses. The group comprises von Recklinghausen's disease (neurofibromatosis), Bourneville's disease (tuberous sclerosis of the brain) and various types of angiomatosis of the brain, eye and skin.

**Von Recklinghausen's Disease.**—Von Recklinghausen's disease is because of its frequency by far the most important member of the group. The dermadromes, tumors and pigmentations are the most common and striking manifestations of the disorder. The tumors may appear as fibromas and neurofibromas which cannot always be distinguished clinically. Particularly the nature of small tumors may be doubtful. In large soft fibromas a wormlike neurofibromatous plexus may be palpable indicating the ill-defined clinical borderline between the two types of lesions.

The *fibromas* are usually soft (*fibromata mollusca*) and indolent, rarely firm. They may vary in number from a few to several thousand. There does not seem to be any site of predilection although the large fibromas seem to arise more often on the eyelids, the buttocks and the labia majora. The tumors may range from pinhead sized nodules, to gigantic growths weighing more than 80 pounds. If such large tumors involve an extremity the term *elephantiasis mollis* is often used. The fibromas may be flush to or raised above the level of the skin and the base may be thin or wide, the tumor accordingly appearing pedunculated or sessile. The covering skin is most often normal in appearance but sometimes it is pigmented, leathery and warty. A peculiar type is represented by fibromas which give the appearance of an empty bag of acrotum-like wrinkled soft thick skin (*pachydermatocoele*). Such flabby tumor formations may be seen on any part of the body surface. Trauma may change them into large and troublesome hematomas. The surface of the fibromas may show comedos or local hypertrichosis. The palms and soles are seldom involved. Spontaneous involution is very rare.<sup>1710</sup>

The *neurofibromas* (neurofibromas) represent the second type of Von Recklinghausen neoplasms. In typical instances they are much firmer than the fibromas and tender on palpation or sometimes spontaneously painful. They are often spindle-shaped or show their neurogenic origin by palpable worm or

<sup>1710</sup>Sealfield, E. and Sealfield, I. Hemifibroma, Recklinghausen, et. Handb. d. H. u. Gk. 12, 2 53-191 1923



plexus-like structures. The neurinomas may develop anywhere along peripheral nerves or in the central nervous system and they too may reach very large sizes.

In one of the cases presented by Jones Jr. and Hart<sup>77a</sup> the mass grew slowly from a small buttock tumor to a size which exceeded half of the entire body of the 36-year-old emaciated man.



Fig. 242—Von Recklinghausen's disease

The *pigmentary* lesions of Von Recklinghausen's disease occur as large and small spots. H. W. Siemens<sup>77a</sup> emphasizes that the large spots differ from the ordinary smooth pigmented nevi. Their edges are smooth and their color is yellowish-brown while the true nevi spili have a more jagged contour and an olive shade. The large Recklinghausen spots range from fingernail to palm-size the larger ones often being oval-shaped and arranged in the direction of the cutaneous lines of cleavage. Their color is best characterized by the often used term *café au lait*. The small spots resemble freckles, but their distribution is even and

<sup>77a</sup>Jones, E. J. and Hart, D. Multiple Neurofibromatosis, *Ann. Surg.* 130: 516-520, 1920.

<sup>77b</sup>Siemens, H. W. Clinical and Dermatologic Studies on Recklinghausen's Disease, *Arch. f. Dermat. u. Syph.* 164: 80-103, 1920.



Fig. 343.—Von Recklinghausen disease



Fig. 344 Von Recklinghausen's disease Empty pouch From Hart (Ass. Surg.)

is not influenced by exposure to light<sup>270</sup> The small spots may be innumerable Pigmented spots of both kinds are hardly ever missed. They may precede other skin manifestations by many years. Ordinary and unusual nevi e.g. the so-called bathing trunk nevus hemangiomas and the nevus anemicus have been noticed in a number of instances.<sup>271,272</sup>

The systemic character of Von Recklinghausen's disease manifests itself in the multiplicity of organic involvements. Abdominal intestinal<sup>27</sup> intra



Fig 215.—Von Recklinghausen disease. Giant fibroma interspersed with pseudo-cystic lesions



Fig 216.—Von Recklinghausen disease. Empty pouches.

<sup>270</sup>Wakley C P III and Weber F P. Generalized Neurofibromatosis With Naevus Anemicus. *Internat. Clin. J.* Ser 46: 144-147 1938

<sup>271</sup>Harton, A. H and Ingram, K. Neurofibroma with Both Cutaneous and Visceral Lesions. *J. Coll. Surgeons, Australasia* 9: 397-403, 1931 *Id.* 39 353.

pleural<sup>176</sup> and mediastinal<sup>176</sup> neurofibromas as well as sciatic nerve tumors, illustrate some of the many rare localizations. Of greater importance are the neurinomas of the central nervous system and of the intracranial nerves. A considerable part of the meningiomas, of the tumors of the spinal cord of the cerebello-pontine angle and of the acoustic nerve belong here.<sup>222, 274-278</sup>

The symptomatology of these central tumors depends on their location. The central neurinomas are usually not malignant although their site may make them extremely dangerous.

Perhaps of greater practical importance than the relatively rare central lesions, are the involvements of the skeleton. Here, too the site is more im-



Fig 317.—Von Recklinghausen disease. Enormous neurofibroma of the hip. (From Hays, *Ann. Surg.*)

portant than the size or number of the lesions which cause cystic destruction and peculiar irregularities in the growth of some long bones as a sequel to epiphyseal or shaft lesions during the growing age.<sup>279</sup> Kyphosis may be an early symptom even before skin lesions are noted. Kyphoscoliosis has been observed

<sup>176</sup>Canigiani, T. Die in rathorakalen Neurofibrome. *Beitragenzur. Ch.* 214-219, 1921.

<sup>222</sup>Mahaim, O. Hentborne, J. O. and Albebach, H. K. Neurofibromatosis With Malignant Thoracic Tumor and Metastasis in Child. *Am. J. Dis. Child.* 57: 281-300, 1932.

<sup>274</sup>Artesti, N. R. E. Rückenmarkstumoren und Neurofibrome. *Anatomie und Embryogenese*, Hirschman and Wiesbaden, 1930, J. F. Bergmann.

<sup>275</sup>Mosbacher, F. W. Recklinghausensche Krankheit od. Tumor cerebri, *Psychiat.-neurolog. Wchnschr.* 1931 II 4: 1-418.

<sup>276</sup>Mosbacher, F. W. Recklinghausensche Krankheit, *Fortschr. d. Neurol. Psychiat.* 2: 279, 1927.

<sup>277</sup>Hillemoriel, J. J. and Thirupont, R. Tumeurs bilatérales de l'acoustique dans la neurofibromatose. *J. belge de neur. et de psych.* 33: 779-785, 1932.

<sup>278</sup>Ferrater, O. and Gapel, O. Zentrale diffuse Schwannose bei Recklinghausenscher Krankheit, *K. Neur.* 131: 116, 1934.

in as many as 43 per cent of some series.<sup>2722</sup> Pseudarthroses of the legs cystic destruction of the hip bones<sup>2723</sup> compression of the spinal cord<sup>2724</sup> and osteomalacia<sup>2725</sup> represent some of the typical skeletal phenomena. Moderate acromegaly<sup>2726</sup> cutis verticis gyrata,<sup>2727</sup> Fröhlich's syndrome<sup>2728,2729</sup> adrenal symptoms<sup>2730,2731</sup> vagus tumor<sup>2732</sup> high blood calcium and potassium<sup>2733</sup> and many other endocrine features<sup>2734</sup> have been recorded without leading to a well founded endocrine theory of the pathogenesis of Von Recklinghausen's disease.<sup>2735</sup> In this connection the unfavorable influence of puberty and pregnancy on the production of tumors must be mentioned. Psychic anomalies including all degrees

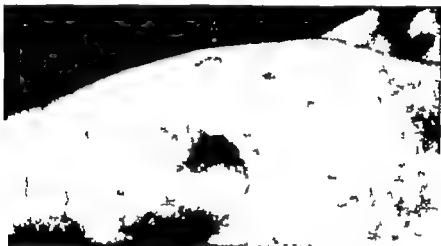


Fig. 348 — Von Recklinghausen disease. Large and small pigmented spots.

<sup>2722</sup>Stalman, A. Nerven- Haut und Knochenveränderungen bei der Neurofibromatose Recklinghausen, Vircho Arch f. Path Anat 229 90-120 1923

<sup>2723</sup>Richter W. Neurofibromatose Recklinghausen mit cystischen Veränderungen in den Hüftgelenkknöcheln. Skd 44 273

<sup>2724</sup>Miller A. Neurofibromatose, With Reference to Skeletal Changes, Compression Myelitis and Malignant Degeneration Arch. Surg 23: 100-122, 1930.

<sup>2725</sup>Osis, H. N. and Driver J. R. Von Recklinghausen Disease Arch. Dermat. & Syph. 23: 782, 1930

<sup>2726</sup>Motz Vogel, H. Die Charakterbildung der Neurofibromatose (Recklinghausen). Dermat. Wechnchr 1933 I 361-363

<sup>2727</sup>Rajka, E. Pachydermia verticis (Cutis verticis gyrata) Marfan Recklinghausen, Skd 44 18 1933

<sup>2728</sup>Rusakov, B. Zur Frage der endokrinen Anomalien bei der Recklinghausenschen Krankheit. Russk. Verh. Dermat. 8 2 1931. Zbl. 39: 315.

<sup>2729</sup>Obertländer K. Zur Frage der Dystrophia pluriglandularis neurofibromatosa, Wien. med. Wechnchr 1931 I 535-539

<sup>2730</sup>Rosenthal, D. B. and Willis, R. A. Association of Chromaffin Tumours With Neurofibromatosis, J. Path. & Bact 43 594-603 1936.

<sup>2731</sup>Levin, O. L. and Behrman, H. T. Neurofibromatosis—Eleven Manifestations and Internal Relations, Arch. Dermat. & Syph. 41: 480-503 1940

<sup>2732</sup>Richter H. Vagustumor bei Recklinghausenscher Neurofibromatose, Deutsche Zeitschr. f. Chir. 237: 63-79 1932.

<sup>2733</sup>Markata, Th. and Mischel, P. Recklinghausen Disease and Ca-Metabolism, Rev. radiol. chn. 1 232-241 1932. Zbl. 43 533.

<sup>2734</sup>Frensd H. Ueber endokrine Störungen bei Recklinghausenscher Krankheit, Arch. f. Dermat. u. Syph. 158: 126-143 1930

of feeble mindedness and frank psychosis<sup>2722, 2726, 2767</sup> are common. Hebra believed "that all patients suffering from fibroma molluscum were mentally retarded individuals. In a modern series<sup>2743</sup> about one-half of the patients showed mental deficiencies.

The patients afflicted with Von Recklinghausen's disease often have a characteristic melancholic, or bored facial expression which Rille<sup>2744</sup> partly ascribes to changes in the facial skin. The eyes and ears participate in the morbid process in many ways. There may be enormous tumors of the lids<sup>2745</sup> and of the



Fig. 348.—Von Recklinghausen's Disease. Small pigmented spots and larger pigmented moles. The patient is only 23 years old, therefore lesions mostly small and not too numerous. (Courtesy Wisconsin General Hospital)

<sup>2722</sup>H. bbe, H. and Rogerson, C. H. Anxiety Aspects Arrata, Neurofibromatosis, Articular Fibrosis. Case, Brit. M. J. 2 486-487, 194

<sup>2726</sup>Sorokovic, V. Symptomatology der Recklinghausenschen Krankheit, Obozr Psichiatr. 4 187-173, 1929 Ebl. 86 773

<sup>2767</sup>Woringer F. Maladie d Recklinghausen, Bull Soc. franc. d. dermat. et syph. 29 1810-1812, 1922.

<sup>2743</sup>Rille. Der Gesichtszusatz, of neues Kennzeichen des Morbus Recklinghausen, Dermat. Wechschr. 1918, II 1413-1 37

<sup>2744</sup>Kaupp, A. A. Von Recklinghausen Disease: Case With Involvement of Left Eyelid, J.A.M.A. 106 494-496, 1932.

acelerae<sup>2770</sup> buphthalmos, changes of the retina and of the optic nerves or their surroundings<sup>2771</sup> and tumors.<sup>2772</sup>

Deafness from bilateral acoustic nerve tumors and other nervous disturbances of hearing are well known and sometimes demonstrable by roentgenographic examination of the petrous bone<sup>2773,2774</sup>

The disease is hereditary though certain factors may be necessary to make the hereditary character manifest. The trouble has been seen as a concordant feature in homozygotic twins<sup>2775,2776,2777</sup> occurring in six generations<sup>2778</sup> and in as many as four siblings.<sup>2779</sup> Among 115 children of Recklinghausen patients 43.5 per cent were afflicted<sup>2777</sup>. H. W. Siemens characterizes the inheritance of Recklinghausen's disease as an irregularly dominant one. Solitary cases without apparent familial connection are not rare. Both sexes are equally affected<sup>2780</sup>. The tendency to malignant degeneration of Recklinghausen tumors may be familial (Hockstra after Moebacher<sup>2781</sup>).

The syndrome occurs in many degrees of severity. Within one family cases with all types of manifestations may be seen together with cases whose only symptoms may consist of some pigmented spots without tumors. Generally the term *formes frustes* is applied to cases with less than the four types of dermadromes: the large and small pigmented spots, the fibromas and the neurofibromas. Apparently abortive cases showing very few lesions may still become severe.<sup>277</sup>

The disease may be congenital but commonly comes on gradually<sup>2770</sup>. At certain periods, however like puberty, pregnancy and the menopause, and after infections like typhoid and mumps the rate of appearance of new symptoms may be stepped up. Since the lesions only come and do not go older patients usually have more than younger patients.

The course of the disease has already been indicated. In advanced age the cases often become more progressive and changeable.<sup>2782</sup>

The life expectancy is generally favorable, but may be entirely changed by complications particularly of the nervous and skeletal systems. Sarcomatous degenerations of (see Charache<sup>2783</sup>) tumors occurs in about 10 per cent<sup>2784</sup> prob-

<sup>2770</sup>Alasch, L. Caso di morbo di Recklinghausen con manifestazioni endocranee rare localizzazioni epidermiche. A. ti Congr. Oftalm. pp. 663-678, 1933. Ebl. 48: 64.

<sup>2771</sup>Weber, F. P. and Dodge, O. B. Recklinghausen Neurofibromatosis With Unilateral Buphthalmos and Multiple Tumors in the Face and Skull. Proc. Roy. Soc. Med. 27: 623-640, 1934.

<sup>2772</sup>Gardner, W. J. and Turner, O. Bilateral Acoustic Neurofibromas. Arch. Neurol. & Psychiat. 11: 78-86, 1940.

<sup>2773</sup>Hilsholtz, G. W., Pendergrass, E. P. and Widmann, B. P. Roentgenographic Findings in Neurofibromatosis. Radiology 25: 701-737, 1940.

<sup>2774</sup>Levy, H. Recklinghausensche Krankheit und cerebrales Syndrom bei einem reinigen Zwillingpaar. Zeitschr. f. menschl. Vererb. Konstitutionslehre 19: 721-730, 1936.

<sup>2775</sup>Loftis, B. L. Neurofibromatosis in Identical Twins. Arch. Dermat. & Syph. 63: 657, 1940.

<sup>2776</sup>Garland, A. Brothers With Neurofibromatosis. Brit. M. J. 2: 120, 1941.

<sup>2777</sup>Freiler, S. A. and Davenport, C. B. Multiple Neurofibromatosis and Its Inheritance. Am. J. 31: 86, 1941. 807-840, 810.

<sup>2778</sup>Clair, J. and Oullevet, F. I cas de maladie de Recklinghausen. Bull. Soc. franç. de dermat. et syph. 48: 335-358, 1932.

<sup>2779</sup>Andrews, O. C. Von Recklinghausen Disease. Arch. Dermat. & Syph. 24: 823-840, 1931.

<sup>2780</sup>Charpe, J. C. and Young, R. H. Recklinghausen's Neurofibromatosis. 31 Cases. Arch. Int. Med. 59: 269, 1937.

<sup>2781</sup>Charache, H. Multiple Neurofibromas With Sarcomatous Transformation and Skeletal Involvement. Arch. Dermat. & Syph. 60: 184-91, 1930.

ably even less frequently. The patient dies with Von Recklinghausen's disease but rarely of it.<sup>1778</sup>

The microscopic structure of the neurinomas shows bandlike zones of parallel elongated nuclei alternating with zones of parallel thin fibers without nuclei. Sometimes the fibrous part is transformed into a dense finely reticular structure, with fusiform and anastomosing cells. Mitoses are very rare. The growth generally has all the characteristics of a benign neoplasm. Most pathologists believe that the neurinoma stems from the cells of the sheath of Schwann thus being of ectodermal origin. The theory of mesodermal nature is defended by a minority, an important argument being the transition into sarcomas.<sup>1779-1780</sup>

No satisfactory method of treatment is known.

Many authors advise against inadequate surgical removal of tumors, because of the danger of sarcomatous degeneration.<sup>167</sup> The removal of one sarcomatous growth may be followed by a distantly located sarcomatous transformation.<sup>1781</sup>

**Tuberous Sclerosis of the Brain**—(Bourneville's Disease) This is a congenital, progressive and often familial condition. It is characterized by epileptic seizures of varying types, mental deficiency, varying from queerness or feeble mindedness to severe idiocy, by eye disorders, and dermadromes. The triad of adenoma sebaceum, epilepsy, and mental deficiency is called *epiloia*. The brain lesions are whitish, relatively firm, well circumscribed plaques and tumors. They are found in varying parts of the cortex, as well as in the ventricles. In the lesions the nerve cells are widely destroyed or damaged by neuroglial proliferation and other processes, among which a certain type of large cell and a tendency to calcification are prominent features. The latter and frequent hydrocephalus, are radiographically demonstrable.<sup>1772</sup> Tumors resembling hypernephromas, rhabdomyomas of the heart, and a variety of other neoplasms may be found. A high basal metabolism,<sup>1776</sup> gynecomastia, precocious puberty,<sup>1773</sup> congenital malformations,<sup>1776,1779</sup> and neurogenic mulberry shaped tumors of the retina<sup>1774</sup> have been described in association with tuberous sclerosis. The disease becomes manifest in early childhood and runs a slowly progressive course. The majority of the patients die before the age of 25 years (Bielschowsky and Gallus after E. Guttmann<sup>1600</sup>).

<sup>1772</sup>Harbata, F. Multiple Neurofibromatosis, Arch. Int. Med. 8: 22-61, 1908.

<sup>1773</sup>Osmond, H. and Kneeland, L. Meningiomas, Springfield, Ill. 1922, Charles C. Thomas.

<sup>1774</sup>Ornstein, A. Metrixome, Handb. d. H. u. Gk. 22, 3: 1923.

<sup>1775</sup>McNairy, D. J. and Montgomery, H. Cutaneous Tumors of von Recklinghausen Disease, Arch. Dermat. & Syph. 51: 244-260, 1948.

<sup>1776</sup>Kreyenborg, G., DeBanco, E. and Haach, K. Tuberous Sclerosis and Adenoma sebaceum, Z. Neur. 128: 326-336, 1930.

<sup>1777</sup>Watrin, J., Maigret, P. and Wallis, R. Case of Bourneville's Tuberous Sclerosis and Symmetrical Fibrous Nevus of Face, Ann. de dermat. et syph. 19: 644-653, 1929.

<sup>1778</sup>Peric, H. Ein Beitrag zu Histopathologie der t. hereditären Tuberösen Hirnerkrankung, Arch. f. path. Anat. 278: 690-790, 1920.

<sup>1779</sup>Kuh, H. Ueber den Ertrag der t. hereditären Sclerosis, zugleich ein Beitrag zur klinischen Diagnostik und Histopathologie dieser Krankheit, Z. Neur. 144: 262-252, 1923, Bid. 48: 249.

<sup>1780</sup>Van Der Hoeve, J. Eye Symptoms in Phacomatosis, Tr. Ophth. Soc. U. Kingdom 57: 290-401, 1912.



The disease has frequently been encountered in families, sometimes in three generations <sup>271, 272, 273</sup> and occasionally together with manifestations of Von Recklinghausen's disease <sup>274, 275, 276, 277</sup> indicating the relationship of these two neurocutaneous syndromes which seem to be caused by unknown factors acting on the ectoderm.



Fig. 240.—Tuberous sclerosis (epiloia). Adenoma sebaceum in typical distribution along the nasolabial folds and on the chin. (From Good, O. K. and Garb, J. Arch. Dermat. 1942.)

**Dermadromes.**—The best known dermadrome of tuberous sclerosis is the *adenoma sebaceum* of the face. This dermatosis consists of more or less raised discrete hemispheric papules which are mainly arranged in the neighborhood

<sup>271</sup>Koesen, J. Eine familiäre, hereditäre Form von tuberöser Sklerose, Acta psychiat. 7: 212-221 1923.

<sup>272</sup>Koesen, J. Eine familiäre hereditäre Form von tuberöser Sklerose, Nederl. tijdschr. geneesk. 1931 I: 721-735.

<sup>273</sup>Borresena, Dyckmann, and Van Bogaert. Formes hérédofamiliales, de la sclérose tuberéuse, J. belge de neurol. et de psychiatrie 22: 712-746 1923. Ebl. 49: 406.

<sup>274</sup>Warther. Morbus Pringle, Morbus Recklinghausen und tuberöse Hirnsklerose, Ebl. 26: 503, 1931.

<sup>275</sup>Battersworth, T. and Wilson, M. J. Tuberous Sclerosis, Dermatological Aspects, Arch. Dermat. & Syph. 43: 1-41 1941.

<sup>276</sup>Bychowski, S. Tuberöse Sklerose, Warschau Onk. 8: 440-463, 1931; Ebl. 26: 186.

<sup>277</sup>Mukai, J. Naevus sebaceus, Acta dermat. (Kyot.) 17: 432-478 1931. Ebl. 29: 554.

<sup>278</sup>Fuhr. Naevus Multiplex Pringle, Ebl. 45: 15.



of the nasolabial and mental folds. The symmetry is marked. The size of the individual lesions ranges from a few millimeters in diameter to almost a centimeter the larger lesions being flatter and usually situated in the center of the group. The papules may vary in color and firmness. In the so-called Balzer type the papules have the color of normal skin in the Pringle type, they are soft and red and in the Hallopeau Leredde-Darier type, they are small and very firm.<sup>272</sup>



Fig. 353.—Tuberous sclerosis. Large fibromatous nevoid growth of the scalp. (From Geod, G. K. and Garb, J. Arch. Dermat. 1943.)

The pathological differences are explained by the prevalence of the sebaceous glands, the vascular elements or the fibrous stroma. Spontaneous regression has been observed in some cases but this is not the rule. The three types may be seen together.<sup>273</sup>

Nevoid slow growing pigmented *plaques* of a size which may cover for example the entire temporal area and keratofibromatous leather like plaques sometimes reaching palm-size have been described.<sup>274,2000,2001</sup> The lumbar region is a favorite site for such nevoid plaques and similar growths. The plaques show

<sup>272</sup>Dobkewitch, R. *Adresses Nouvelle Pratique Dermatol.* Vol. VI Paris, 1936, Masson & Co.

<sup>2000</sup>Sachs, M. D. and Shaskan, D. A. Tuberous Sclerosis, *Am. J. Roentgenol.* 82: 25-39, 1944.

<sup>2001</sup>Kurtz, L. Tuberous Sclerosis, III *Veränderungen, Dermat. Wchnschr.* 1934, I, 357-365.

pathologic changes similar to the adenomatous papules. They are not of the same diagnostic importance as the adenoma sebaceum. <sup>787,788</sup>

Slow growing multiple para ungual fibromas of small pea size, especially of the toes<sup>789</sup> have recently become known as a dermatome of tuberous sclerosis. The lesions which have a keratotic top bleed easily and may become troublesome. These tumors find their mucosal equivalent in lobulated fibromas of the gums.<sup>779,790</sup> The nail substance may appear thickened or grooved lengthwise.<sup>791</sup>



Fig 344.—Adenoma sebaceum. (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)

Lipomas syringocystadenomas and some of the skin lesions known to occur in Von Recklinghausen's disease have also been found occasionally in tuberous sclerosis.

Frequently the adenoma sebaceum makes its appearance in the first decade of life<sup>778</sup> possibly stimulated by the same hormonal factor which causes the development of the sebaceous glands.

<sup>787</sup>Van Boven, H. *Hautkrankheiten* 7: 8. Formen familiäre der tuberösen Sklerose. J. belge de Neurol. et de psychiat. 32: 687-712, 1933. Ed. 68-404.

<sup>788</sup>Kurtz, L. Tuberöse Sklerose mit Hautveränderungen (subunguale Fibrome, Fibrome und Zysten, Rosaceen des Gesichts und lymphogeknotete Fibrome an der Glottis). Ed. 43: 730.

<sup>789</sup>Loew, H. B. Nagel-, Haut- und Allgemeinerkrankungen, Med. Klin. 36: 479-491, 1940.

**Angiomatosis cerebri**—Hemangiomas of the brain are frequently<sup>2772,2788</sup> associated with vascular nevi of the face. While the nonactive nevus-like hemangiomas are apt to be found in the cerebrum, the growing angioblastomas usually develop in the cerebellum. Only the former seem to have related skin lesions, while both develop eye manifestations, though of different types. The nervous symptoms usually start very early, sometimes during the first months of life.<sup>2787,2793</sup> Contralateral jacksonian fits, vertigo, tremor, disturbances of the gait, and hemiplegia<sup>2800</sup> are the most obvious symptoms. Idiotcy has also been observed.<sup>2807</sup> The brain lesions may calcify and thus produce roentgenologic pictures<sup>2772,2795</sup> consisting of whorls and sinuous deposits in the gyri of the frontal and temporal lobes. Asymmetry of the face<sup>2772,2808</sup> may accompany the unilateral brain changes.

The accompanying vascular nevi mainly occupy the face. They seem to be more often unilateral than bilateral. They are large, even enormous<sup>2811</sup> single



Fig. 844A.—Fibroma of the nares in tuberous sclerosis and adenoma sebaceum. (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)

<sup>2788</sup>Krabbe, K. R. Facial and Meningeal Angiomatosis With Calcifications of the Brain Cortex. *Arch. Neurol. & Psychiat.* 23: 737-758, 1934.

<sup>2789</sup>Kufz, H. Ueber hereditäre Angiomatose des Gehirns und der Retina. Ihre Beziehungen zu einander und zur Angioma cerebri. *Ztschr. f. d. ges. Neurol. Psychiat.* 112: 631-660, 1933.

<sup>2790</sup>Meyer, F. Gesichtshautangiome und Gehirnhämangiome. *Monatsschr. f. Psychiat. Neurol.* 92: 294-306, 1936.

<sup>2791</sup>Schaefer, W. Ueber einen Fall von halbseitigen Hirn- und Hautangiomen. *Monatsschr. f. Kinderh.* 59: 33-44, 1931.

<sup>2792</sup>Kreyenberg, G. and Hansing, I. Hauthamangiome mit Rindenangiomen des Gehirns und Hydrophthalmos. *Z. Neurol.* 193: 761-768, 1935.

<sup>2793</sup>Schwartz, O. W. Vascular Tumors and Anomalies of the Skull and Brain. From: *Roentgenological Viewpoint*, *Am. J. Roentgenol.* 41: 881-900, 1939.

<sup>2794</sup>Ironsides, R. and Hill, D. Cutaneous Naevus With Buphthalmos and Epilepsy. *J. Med. Sc.* 67: 631-634, 1941.

or multiple telangiectasias of port wine stain or tumor type sometimes involving the oral mucosa and even the pharynx.<sup>2613</sup>

The nevi are often but not necessarily on the side of the hemangioma of the brain.<sup>2613,261</sup>

Besides the telangiectatic lesions nevus anemicus has been recorded in several instances.<sup>2614</sup> Pigmented nevus of one side of the face and ipsilateral glioma has been seen by Melrowsky.<sup>2615</sup>



Fig 345B —Tuberous sclerosis. Fibromas of the palpebrae with grooving of the skin. (From Moon, *E H Arch. Dermat.* 9:44.)

Heredity is an etiological factor.<sup>2616</sup> Occasional combinations with the other neurocutaneous diseases have been reported.<sup>261 2617,2618</sup>

The term Parkes Weber's syndrome is sometimes used for the combination of cerebral and cutaneous hemangiomas with epilepsy and idiotism.

<sup>2613</sup>Tyson, R. H. Nevus Flammeus of the Face and Globe Associated With Glaucoma, Vascular Changes in the Iris and Calcified Vascular Growth in the Left Occipital Lobe With Right Hemispheric Hemianopsia. *Arch. Ophth.* 9: 365-371 1922

<sup>2614</sup>Kline, R. W. D. Trigeminal Nevus and Hemangioma of Meninges. *Proc. Roy. Soc. Med.* 25: 1722-1724, 1932.

<sup>2615</sup>Weber, F. F. and Harris, R. E. A Case of Widely Distributed Superficial Telangiectatic Nevus Associated With Areas of Nevus Anemicus. Indications That Portions of the Cerebral Meninges are Similarly Involved. *Brit. J. Dermat.* 45: 77-82 1932

<sup>2616</sup>Melrowsky E. Hafterförmiger Nevus bei einem Epileptiker. (Sektionsbericht.) *Zbl. 40: 24*

<sup>2617</sup>Touraine A and Nguyen-Van-Vang. Éta dysraphique familiale. *Bull. Soc. Franç. de dermat. et syph.* 43: 1650-1661 1926

<sup>2618</sup>Orridge, H. M. Case of Meningeal Nevus Associated With Adenoma Sebaceum. *Edinburgh. M. J.* 20: 102-111, 1923

## CHAPTER XXXIX

### DISORDERS OF THE NERVOUS SYSTEM

#### *Diseases of the Spinal Cord*

Cord lesions may regardless of their nature produce *pigmentations*. Such melanoses in the area of the skin supplied by the injured parts of the cord have been observed after gunshot injuries during the first world war. André Thomas<sup>122</sup> found an increase of the pilomotor and sudomotor reflexes in the pigmented areas which suggests that the sympathetic system plays a part in the etiology of the pigmentations. The pigmentations may appear after two weeks (Simons after E. Kaufmann<sup>123</sup>) or after months or even years. Sézary<sup>124</sup> feels that the slow appearance of the lesions makes a sympathetic etiology unlikely. Since most of the cord injuries are fatal before the pigmentation has a chance to develop observations have remained rare. Depigmentations of the skin after injuries or other lesions of the spinal cord e.g. tumors have occasionally been seen.<sup>125 126 127</sup> In one case there was red dermographism above and white dermographism below the level of the injury.

E. Guttman<sup>128</sup> points out that the fibers conducting the sensations of touch and position ascend directly without crossing while the pathways for the perception of warmth and pain enter a second neuron and cross to the other side. This explains the fact that a unilateral lesion of the spinal cord causes a contralateral anesthesia for warmth and pain. Localized destruction of the gray matter of the cord also causes abolition of the perception of warmth and pain with preservation of the senses of touch and position. This dissociation can be seen in several localized cord lesions e.g. in syringomyelia hemorrhage into the gray matter and in intramedullary tumors. The sensibility above and below the level of a circumscribed intramedullary lesion may be undisturbed if no direct fibers are involved. Complete transverse lesions of the spinal cord leads to anesthesia below the level of the corresponding cutaneous innervation. The lowest segments, however often retain some sensibility.

**Status Dysraphicus.**—Status dysraphicus<sup>129,130</sup> is a hereditary condition characterized by a great number of malformations. The name is derived from the pathogenesis of the leading anomaly, *spina bifida* caused by failure of the embryonal closing of the raphe of the medullary groove. Funnel chest disproportion between trunk and extremities, abnormally long arms clubbed hands

<sup>122</sup>André-Thomas. La pigmentation de la peau dans les blessures et les affections de la moelle. Rev. neurol. 28 103-108 1931.

<sup>123</sup>Dresner F. W. Untersuchungen zur Ätiologie der Syringomyelie. Status dysraphicus. Deutsche Zeitschr. f. Nervenk. 88 1 1936.

<sup>124</sup>Dresner F. W. Pathol.-anatom. Begründung des Status dysraphicus. Deutsche Zeitschr. f. Nervenk. 89 104, 1937.

and clubbed feet polymastia asymmetry of the breasts and web formation are some of the stigmata. Debility epilepsy psychoses acrocyanosis cataract hypogenitalism Horner's syndrome heterochromia of the iris and other disturbances may accumulate in one individual but more often such symptoms are grouped in families.

Spina bifida occulta occurs in about 17 per cent of all persons a fact which has become known only with the advent of the x-ray.<sup>2201</sup> Lumbar nevi and circumscribed sometimes excessive hypertrichosis over the spine may indicate the underlying cleft formation.



FIG. 236 Trophic sore after spinal cord lesion and operation

**Familial Trophedema.**—There also exists a relationship between status dysraphicus and the chronic *familial trophedema* of Nonne Millroy and Meige.<sup>2202, 2203</sup> This is a hereditary condition which has been observed in as many as five generations,<sup>2204, 2205</sup> though never in many members. The disorder affects

<sup>2201</sup>Carthas H. and Larras J. Klinisch-erbblologische und röntgenologische Untersuchungen an Fällen von Status dysraphicus und 17 Fällen von Myelomeningocele. *Klin. Wochenschr.* 149: 4, 1933.

<sup>2202</sup>Leves. Les formes de la Trophedema Meige-Millroy. *Dermat. Weimarer* 36: 777-782, 1932.

<sup>2203</sup>Jarowick W. Familiäres Trophedema und plus bifida occulta. *Dermat. Weimarer* 152: 622-644, 1931.

<sup>2204</sup>Meige P. Meige syndrome. *Rev. radiol. clin.* 8: 8, 933, 1934.

<sup>2205</sup>Meige P. Dystrophie cutanée héréditaire. *Presse méd.* 3: 1, 1936.

<sup>2206</sup>Meige P. Les formes de la Trophedema Meige-Millroy. *Dermat. Weimarer* 36: 777-782, 1932.



the female sex more frequently than the male.<sup>1874-1917,1918</sup> The trouble is sometimes congenital but more often it starts later in life frequently in adolescence rarely later. A slowly progressive later stationary edema develops in one or both legs rarely in the arms. Painful febrile attacks have been observed to increase the edema.<sup>1919,1920</sup> The fully developed lesion consists of an enormous firm edema. The skin is smooth white or bluish or with a vascular pattern and feels cool. Folds cannot be raised. The contour of the legs is usually com-



Fig. 837.—Pnch of hair over spine bifida.

pletely lost. A deep fold separates the leg from the foot. The condition does not endanger life as shown by Meigs's second report on the same case 35 years after his first presentation. At the time of the second report, the afflicted woman was 75 years old without other trouble than the edema.

<sup>1874</sup>Meigs, E. Sur le trophodème chronique de Meigs—Nouveaux cas—Considérations sur leur étiologie, *Rev. Neurol.* 23: 1094-1095, 1921.

<sup>1889</sup>Thayer, E. Mieroy Disease, *Arch. Dermat. & Syph.* 23: 1127-1128, 1921.

<sup>1919</sup>McGuire, J. and Zeek, P. Pathogenesis of Chronic Hereditary Edema of Extremities (Mieroy's Disease), *J.A.M.A.* 76: 870-872, 1922.

Besides status dysraphicus hypothyroidism<sup>1904,1905</sup> hyperthyroidism<sup>1902,1922</sup> hypogonadism<sup>1902,1922</sup> and melorheostosis Léri<sup>1928</sup> have been found in association with the edema, but no definite etiology has been established. The dominant pathological feature is loss of the subepidermal elastica increase of collagenous fibers and widening of the lymphatic spaces. No effective therapy is known.



Fig. 256.—Spina bifida. X-ray of patient. Its patch of hair over lumbar spine.

Syringomyelia is much more closely related to status dysraphicus. Curtius and Lorenz<sup>1928</sup> found among 17 cases of syringomyelia 11 instances of spina bifida occulta. In the families of patients afflicted with syringomyelia anomalies of the breasts and mental disorders are relatively common.

Increase of neuroglia (gliosis) in the spinal cord and formation of tube-like cavities within these lesions lead to a great variety of neurological symptoms.

<sup>1904</sup>Neumann-Brosner, A. Trophodermia (Melorheostosis). *Ann. EP.* 5:46, 1924.

<sup>1905</sup>Patricik, E. Melorheostose (Krankheit). *Cong. dermat.* 12: 284-290, 1921. *Id.* 49: 426.

<sup>1928</sup>Oschisching, F. Ueber eine Kombination von Trophodermia (Melorheostose) Léri.

*Dermat. Wchnsch.* 69: 1761-1766, 1929.

<sup>1922</sup>Slasman, A. H. Ein Fall von Trophodermia chronica faciei in einem Hereditäre zur Situation. *Ann. EP.* 27: 1927.

varying with the sites within the central nervous system. There occur sensory disturbances, muscular atrophy beginning in the intermetacarpal muscles of the hands and ending up in characteristic contractions, skeletal damage, eye symptoms, and spasms. The course of the disease is very slow, the first symptoms usually remaining unrecognized over several years. The patients rarely die of syringomyelia but they often succumb to intercurrent infections.<sup>104</sup> Recovery hardly ever occurs.



Fig. 350.—Nouveau-Lorge-Milroy disease. Female aged 43 years. Obesity and pituitary symptoms, swelling of legs from childhood, became worse at puberty. Mother had the same trouble. (Courtesy Wisconsin General Hospital.)

**Dermadromes**—The dermadromes of syringomyelia are mainly due to the fundamental disturbance, dissociated anesthesia. While the perception of pain and temperature become lost, the sense of touch and deep sensibility remain undisturbed. Paresthesias are common in the early stages, and the attempt to treat them with heat has often caused the first painless burns; circulatory and possibly trophic influences may also play a part.

The patients hardly ever escape the traumatic and infectious complications. In advanced cases the hands are rarely found free of crusty sometimes rhagadi form ulcerations of varying sizes often located on the extensor surfaces of the fingers. Such trophic ulcers may lead to painless, destructive lesions around the nails. Mutilation resembling leprosy may ensue. These fairly characteristic finger affections are called *panaris analgésiques*. Transitory edema of the Quincke type<sup>1534,1535,1537</sup> as well as lasting swellings represent another feature. These swellings are often found on the hands giving them a succulent appearance. The edema may disappear and leave a flaccid atrophic skin with a silky or papyraceous surface, or it may lead to a leathery uneven hypertrophy and hyperkeratosis unrelated to pressure or work (lizard skin). The appearance of unusual keratosis on the hands should make the physician think of syringomyelia. Regional<sup>1538</sup> eruptions of large bullae in moderate numbers and unrelated to trauma may cause necrotic ulcerations<sup>1539,1540</sup> another parallel to leprosy.

The nails may become affected in many ways. Hypertrophy and atrophy anomalies of position white color brittleness, groove formation and complete loss have often been described<sup>1541,1542</sup>. The hair may gray early.

The treatment is symptomatic. Protection from trauma especially burns is most important.

No skin manifestations were observed in 81 cases of amyotrophic lateral sclerosis<sup>1543</sup> though symmetric pigmentations of the forearms had been described earlier (Bowring after E. Kaufmann<sup>1544</sup>).

### Diseases of the Brain

A variety of dermatomes may be seen as results of cerebral lesions.

Apoplexy may be followed by unilateral sweating of the paralyzed side (Binger and Berg after Marchionni<sup>1545,1546</sup>). This has been called *hémiplegie sudorale*. The galvanic skin reflex (Veraguth Tarchanoff's phenomenon) can not be elicited on the paralyzed side.<sup>1547</sup>

Localized or unilateral swelling dryness, and in about half of the cases scaliness, occur. Unilateral jaundice<sup>1548</sup> occurs in *apoplexy* (See Chapter on Liver).

<sup>1534</sup>Schäfer O. Hyperkeratosen der Handteller als Früherkennung bei Syringomyelie. Arch. f. Dermat. Syph. 173 37-33 1935

<sup>1535</sup>Syromons L. Présence les d'une maladie atteint de ganglions cutanés d'origine syringomyelique. Rev. méd. de la Soc. 49: 280, 192. Ekt. 25 86.

<sup>1536</sup>Garney R. E. Syringomyelia Associated With Trophic Destructive Bullae. Arch. Dermat. & Syph. 33 104-109 1936

<sup>1537</sup>Frühwald Syringomyelie Ekt. 48 287

<sup>1538</sup>Wechsler J & Papirsohn M. R. and Stein, A. Primary and Symptomatic Amyotrophic Lateral Sclerosis. (Cases) Am. J. M. Sc. 236 70-81 1944

<sup>1539</sup>Esner, K. W. and Podetz H. R. Able f. des galvanischen Hautreflexes bei Halbseitigen Hirnleiden. Deutsche Zeitsch. Nerven. 128 21-42, 1935

<sup>1540</sup>Page J. H. Ipsilateral Erythema and Contralateral Jaundice Associated With Hemiplegia and Cardiac Decompression. Am. J. M. Sc. 177 373-378 1929.

*Brain injuries* may cause contralateral coating of the tongue,<sup>212,213</sup> alopecia<sup>197</sup> and sudden unilateral graying of the hair and beard (Gowers after J.A.M.A.<sup>214</sup>)

Wartenberg<sup>215</sup> observed isolated pruritus of the nose in *tumors* of the temporal lobe. He considered the itching and compulsory scratching of the nose, which persisted in deep sleep as a valuable temporal lobe symptom but other neurologists<sup>216</sup> deny its localizing value.

Other occasional observations are unilateral seborrhea and sweating ecchymoses vitiligo and other pigmentary disorders of the skin<sup>217,218</sup> (See also neurocutaneous diseases)



Fig. 300 - Unilateral edema of the face on paralyzed side. Three years after hemiplegia.

Urticaria factitia<sup>219</sup> is supposedly pronounced in idiopathic *epilepsy* but not in the jacksonian type. During the epileptic fit the galvanic skin resistance is reduced.<sup>220</sup>

The epileptic seizure may be preceded by vasomotor symptoms like blushing or pallor. The acute spasms of the respiratory muscles and the concomitant increased pressure in the vena cava may cause petechiae.

These are often found in the conjunctivae and in the skin of the neck, the chest and behind the ears.<sup>221</sup> The petechiae are rarely numerous (ecchymotic mask)<sup>222</sup> but they have some diagnostic or forensic value.<sup>223</sup> Chloasma in the shape of the forehead ring occurs occasionally in epilepsy. (See Encephalitis.)

<sup>212</sup>Börnstein, W. Trophische Veränderungen in der Kaugeschleimhaut (hardgekauter Kaugrubel) bei cortikalem Herd, *Z. Neur.* 104: 776-790 1926.

<sup>213</sup>Levinson, E. U. vollständiger Kaugrubel als vasomotorisch-trophisch. *Sitzungsber. Deutsche. med. Gesellsch.* 83: 1: 707-708 1936.

<sup>214</sup>Vitellius and Human Gray Hair. Editorial, *J. A. M. A.* 122: 878-879 1912.

<sup>215</sup>Wartenberg, E. Ein Schlafwappensymptom, *Arch. f. Psychiat.* 263: 231 1935.

<sup>216</sup>Camilleri, A. F. Diagnostische Wichtigkeit des Schweißes oder urticariformen Dermographismus in der Neurologie, *Acta. Conf. Int. Amer. Neur. sci.* 2: 98-110 1929. *Ed.* 23: 185.

<sup>217</sup>Porter, J. M. J. Galvanic Skin Phenomena in Epilepsy, *J. Gen. Psychol.* 11: 34-44, 1924.

<sup>218</sup>De Blas, A. Sulle così det. macchie ecchymotiche, *Ann. Ital. di chir.* 13: 483-510 1924.

<sup>219</sup>Milieu, G. Piqueté peripartique cervico-thoracique des crises convulsives, *Rev. franç. de dermat. et de vénér.* 4: 127-128, 1928.

*Tramatisation* of the central nervous system may cause *purpura* of a distribution which is apparently governed by the nervous system. Purpura up to the level of a spinal anesthesia,<sup>330</sup> or generalized symmetric purpura after skull fracture<sup>331</sup> pertain here.

Purpuric lesions have been described in many organic diseases of the central nervous system especially in multiple sclerosis.<sup>332</sup>

Diffuse *hypertrichosis* has been observed in encephalitis following *complicated fractures*<sup>333</sup> in glioma of the temporal lobe<sup>334</sup> in disseminated sclerosis,<sup>335</sup> and in several other lesions of the brain. Hirsutism of this type may disappear with recovery.

Encephalitis lethargica (Von Economo's disease) is an epidemic and contagious disease probably caused by a filterable virus. After an incubation period of approximately a week the disease breaks out with mild fever and influenza resembling symptoms often with icterus.

Meningitic symptoms are lacking or mild but ocular palsies and headache develop frequently.

In the course of a week sleepiness or irritability increases. In the lethargic type the patient sleeps most of the daytime. He can be aroused only with difficulty. At night he is often restless. In the irritable or hyperkinetic form the muscle tone is increased. Tremor, spastic paralysis, fever and delirium are the main symptoms. The acute stage may last several weeks or months. The mortality of the cases with a stormy onset may be as high as 33 per cent.

Another third of both types may recover completely and one third develops progressive or stationary sequelae among which Parkinsonism with paralysis agitans-like symptoms rigidity salivation tremor is the most common one (Von Economo after Bing and Haymaker<sup>336</sup>).

In young individuals change of character hypomania and psychoses may follow. The pathological characteristics are inflammatory infiltrations and hemorrhages in the gray matter of the large nuclei and the frontal lobes.

*Dermadromes*—Best known among a variety of skin manifestations of encephalitis lethargica is the profuse *seborrhea*<sup>337</sup> which has been found in from 35<sup>338</sup> to 48 per cent (Stern after E. Guttmann<sup>339</sup>) of the cases. Rattner<sup>340</sup> found unusual oiliness of the face in only 8 per cent. This symptom has rarely been seen in true paralysis agitans.

<sup>330</sup>Ross, F. Purpura nach Lumbalanästhesie. Klin. Wchnschr. 1931 II 3541-3542.

<sup>331</sup>Kändler W. Zur Frage der Purpura traumatica, München, med. Wchnschr. 75 822-824, 1929.

<sup>332</sup>Schindler K. Nervensystem und postane Histamine, Berlin, 927 S. Karger.

<sup>333</sup>Caerapostoli G. B. Sindromul necroticilor con retrobulboure catalasea ed hipertrichosi, Cerrallo 1891 II 28 1931.

<sup>334</sup>Markoff K. Hirsutism in Woman With Glioma of Left Lobe of Brain, Schweiz. med. Wchnschr. 69 45-47 1939.

<sup>335</sup>Levinson E. Ueber Entwicklung von Hypertrichosis bei erblicher multipler Sclerose. Z. Neur. 122: 499-509 1939.

<sup>336</sup>Cole, T. Encephalitis ohne Lethargie während der Grippeepidemie. Eld. Year 29 200, 1930.

<sup>337</sup>Wickman, F. B. Seborrheic Dermatitis in Post Epidemic Encephalitis. Arch. Dermat. & Syph. 21 600, 1930.

<sup>338</sup>Rattner H. Changes in the Skin in Chronic Encephalitis. Arch. Dermat. & Syph. 21: 24-37 1932.

In typical cases the face appears as if it were covered with grease. If the grease is wiped off it reappears within about 20 minutes. Facial puffiness<sup>1236</sup> and complicating seborrheic dermatitis is not uncommon<sup>1237</sup> Seborrhea is comparable to other disorders of secretion like hyperhidrosis and excessive salivation and lachrimation which may cause chronic blepharitis and dermatitis of the lids. The cause of the seborrhea is supposedly an inflammatory irritation of a center in the wall of the third ventricle<sup>1238</sup> Perutz<sup>1239</sup> could produce seborrhea in rabbits by stimulation of the interbrain.

*Trophic ulcers*<sup>1240</sup> mostly in the nasolabial folds or around the nasal orifices sometimes invading the nasal septum and the upper lip have often been described.<sup>1241</sup> The lesions may be very destructive and hard to cure.



Fig. 361



Fig. 362

Figs. 361, 362.—Brow-forehead ring in ophthalmia lethargica. (Courtesy Prof. H. HANSEN, Copenhagen.)

These postencephalitic ulcers have in some instances been mistaken for rodent ulcers. The sensitivity of pain and touch is preserved. Analogous ulcerations in other areas e.g. the hands<sup>1242</sup> and the tongue (Schurmer and

<sup>1236</sup>Stüder H. ( ) Seborrhoea faciei als ein Symptom der Encephalitis lethargica. *K. Natur* 72 454, 1931. (b) Seborrhoea faciei als isoliert: postencephalitische Veränderung. *Wien klin. Wchnschr.* p. 234, 1934.

<sup>1237</sup>Perutz, A., Lesig, B. and Klein, A. E. Karren haben Regulierung des Fettstoffwechsels der Haut. *Arch. f. Dermat. Syph.* 170: 311-320, 1934.

<sup>1238</sup>Hoffman, H. Large Trophic Ulceration of Nose and Mouth Following Lethargic Encephalitis (Parkinsonism). *Deutsche med. Wchnschr.* 57: 228-229, 1932.

<sup>1239</sup>Rosenthal, S. J. and Solovay, J. Trophic Ulcer Following Encephalitis Lethargica. *Arch. Dermat. & Syph.* 59: 535-538, 1939.

<sup>1240</sup>Michon, P. Troubles trophiques cutanés et parkinsoniens localisés. *Bull. Soc. franç. de dermat. & syph.* 28: 1033-1034, 1931.

Baumann after Marchionini<sup>1903,1905</sup>) are much rarer. The localization in the nasolabial folds suggests a connection with the seborrhea which is most active in this site.

*Chloasma*<sup>1904</sup> especially in the form of the brown forehead ring has been found repeatedly<sup>1904,1906</sup>. Such chloasmatic pigmentations are also known to occur in other intracranial processes e.g. epilepsy. The typical brown forehead ring has the shape of a crossbow closely paralleling the hairline in the center and descending symmetrically toward both lateral ends of the eyebrows. A nonpigmented zone separates the hair as well as the eyebrows from the lesions.

Other reports on postencephalitic dermatoses include symmetrical gangrene<sup>1903,1905,1906</sup>, urticaria factitia, Quincke's edema,<sup>1906</sup> multiple paronychia (Schirmer after Marchionini<sup>1903,1905</sup>) severe subungual hemorrhages<sup>1907</sup> diffuse alopecia resulting in almost total baldness in 4 cases<sup>1904</sup> bullous eruptions<sup>1906</sup> and Herpes Zoster<sup>1904</sup> in 16 cases.

<sup>1903</sup>Hachisuwa, H. Skin Changes Following Encephalitis Lethargica, *Acta dermat. venerol.* 33 404-416 1933

<sup>1904</sup>Anderson, O. and Weyers, T. B. Der braune Stirnring, *Ugeskr. f. Læger* 1930 II 817-831 *Zbl.* 86: 214

<sup>1905</sup>Dückler P. Vasomotorisch trophische Störungen bei Encephalitis epidemica, *Gyógyászat* 51 718, 1923 *Zbl.* 23: 174.

<sup>1906</sup>Von Peor P. Hämatom des Nasenbittes bei postencephalitischen Parkinsonismus, *Dermat. Wechnchr* 1931 I 46

<sup>1907</sup>Guérin G. La Klinik der Encephalitis lethargica, *Wien. klin. Wechnchr* 33 226-232 1930

<sup>1908</sup>Vetter A. 16 observations d'zones d'encéphalite léthargique *Zbl.* 36 213



## CHAPTER XL

### PSYCHOSES AND PSYCHODERMATOSES

#### Psychoses

Kretschmer's<sup>2576</sup> work on physique and character correlated schizophrenia and the schizothymic personality with the asthenic and athletic builds and the circular psychoses with the pyknic type. Though many of Kretschmer's "affinities" have been disputed<sup>2577</sup> the cutaneous dermatromes observed by him have to some extent been confirmed by his opponents.<sup>2578</sup> This is particularly true of the hair growth in the main types of psychoses. In the circular group a tendency toward hirsutism is striking. These patients frequently have marked lanugo and axillary and pubic hair. The men have a well developed beard growth of soft texture and equal distribution. The hair often seems lighter during the stuporous period and becomes darker or reddish in the stage of excitation. Such color changes were noticed as early as on the first day of the mental change.<sup>2579</sup> In a 21 year-old blonde woman the hair became partly white during several attacks of dementia praecox but it turned normal again when the spell ended.<sup>2578</sup>

Male baldness seems to be more common among the circular than in the schizophrenic group and there is a difference in the character of the baldness. The circular pyknic<sup>2579</sup> has pronounced temporo-frontal calvities. If he is bald the baldness is shiny and sharply bordered. Kretschmer calls it a "beautiful bald pate." The baldness of the schizophrenic is usually less complete ill defined and irregular.

There is a tendency to formation of folds in the scalp. *Cutis verticis gyrata* and other acromegaloid traits, have been found in schizophrenics by several observers.<sup>25</sup> <sup>2578</sup> The head hair of the asthenic or athletic schizophrenic is often coarse in comparison with the soft hair of the pyknic circular. On the forehead as well as on the nape of the neck the hairline is often straight and there is no temporo-frontal notch. Frequently it is lower so that a *fur cap* type of head hair results. Bridges of hair from the head to the eyebrows and down to the lanugo of the back have been frequently found.<sup>2679</sup> Junction of dense eyebrows (Synophris) occurs occasionally. The terminal hair of the male schizophrenic is relatively weak, though often coarse while the female schizophrenic has a tendency toward

<sup>2576</sup>Kretschmer, E. *Körperbau und Charakter* ed. 2, Berlin, 1923, Julius Springer.

<sup>2577</sup>Betz, D. J. Somatology of the Schizophrenic Patient, *Human Biol* 11: 183-224, 1942.

<sup>2578</sup>Koels, A. Körperbaustudien bei Psychosen. Die männlichen Eirkulären, *Arch. f. Psychiat* 115-150 1926.

<sup>2579</sup>Klier, J. J. Neurogenic and Psychogenic Disorders of Skin, *M. J. & Rec.* 329: 481, 484-618 1929.

<sup>2578</sup>Finkelstein, D. A. *Cutis verticis gyrata* bei akromegaloiden Katatonien, *Monatsschr. f. Psychiat.*

*Neurol.* 106: 104-108 1942.

<sup>2579</sup>Tomasello, A. Rara anomalia del cuoio capelluto "rughe piliche" in un demen praecox *Arch. di antropol. crim.* 55: 1004-1012 1913 Xbl 84 104.

hirsutism.<sup>276</sup> The latter observation is in contrast to Kretschmer. However there is a general impression that some degree of hirsutism is found relatively often in various psychoses.<sup>2277 2278</sup>

■ *Alopecia totalis* may occur in connection with depression<sup>2279</sup> however the depression may also be of a reactive character due to the disfiguring loss of hair.

Heller<sup>228</sup> was unable to confirm earlier claims of unexplainable and characteristic nail changes in psychoses. It is an old belief that the insane have long or unusual nails but this is not true.\* The transverse lines can usually



Fig. 267 Mental retardation. Fur cap half line (Courtesy Wisconsin General Hospital.)

be traced to intercurrent disorders. Under proper care the nail of the inmates of asylums may be in better condition than the nails of the average population.

Repeated loss of the nails and of the hair in circular psychosis has been described (Transfontaines after Heller<sup>228</sup>).

The same hour was the bag fulfilled upon Nebuchadnezzar and he was driven from men, and did as grass as corn, and his body as wet with the dew of heaven, till his hairs were grown like eagles feathers and his nails like birds claws. Daniel, IV 22.

<sup>2276</sup>Mumford H. B. and Cheveau, L. C. F. An Investigation of the Physical Characteristics of the Skin in Some Types of Psychosis, *J. Men. Br.* 78: 242-372, 1922.

<sup>2277</sup>Kliks H. E. Comparison of Non-psychotic Women With Schizophrenics With Respect to Body Type, Signs of Autoimmune Imbalance and Menstrual History, *Psychiatric Quart.* 19: 17-22, 1911.

<sup>2278</sup>Eprints, A. L. Some etiological studies in Psychiatry, *Am. J. Neur.* 162: 276-299 787 1922.

<sup>2279</sup>Parham, C. J. Balfour C. and Caveman, E. Étude anatomopathologique sur les cas de virilisme mâle, *Rev. franc. d'endocrinol.* 2: 72-105, 1923. *Idem* 19: 497.

<sup>2280</sup>Aden, L., and Carlyle-Gall, L. Depression-Hypotrichia-Alopecia-Syndrom, *Brit. M. J.* 2: 67-68, 1942.

The observations on the status of the skin in the insane have not yielded many tangible results. Vascular symptoms are first on the list. Kretschmer<sup>2479</sup> also Mumford and Chevens<sup>2480</sup> emphasize the rosy complexion of the circular pyknic in comparison with the pale asthenic schizophrenics.

The vasomotor lability of the pyknic also expresses itself in a greater tendency to blushing and rosacea. Some authors found the skin of the circular in good condition rather moist with a well developed panniculus adiposus. The skin of the schizophrenic is usually paler flaccid and unhealthy. Acne is frequent.<sup>2481</sup> Dryness and a keratotic tendency has often been considered a characteristic of the skin of the insane.<sup>2482</sup> Mumford and Chevens<sup>2483</sup> relate this symptom to the schizophrenic.



FIG. 264.—Mental debility. Female aged 43 years. Hypertrichosis.

The most important vascular phenomenon of the schizophrenic is *acrocyanosis*. This has been confirmed by many writers.<sup>2479,2484,2485</sup> Closely related to the acrocyanotic syndrome is the pseudo-edema of the insane (Dide Trepeau Kraepelin after Simon<sup>2486</sup>). In acrocyanosis the *acra* are bluish with red vascular patterns cold slightly swollen but not pitting. The swelling may reach up to the knees and a fold may be marked at the ankles and at the base of the toes. There is prolonged white dermographism with red borders, lasting from one and a half to two hours.

Red dermographism is common in a great variety of psychoses.<sup>2484</sup>

Generalized Addisonoid *melanoderma* in catatonic schizophrenia has been observed in several instances.<sup>2487</sup>

Spontaneous and unexplained bullae with subsequent ulcerations, occur even in bedridden patients without undue exposure to traumatism. In the *mentally deficient* anomalies of the hair pigmentation acrocyanosis, pseudo-

<sup>2479</sup>Goldblatt H. and Berman S. Sur la sécheresse de la peau chez les aliénés, *Arch. f. Neurol. & Psychiat.* 18: 324-341 1935.

<sup>2480</sup>Mumford, E. A. Etiology and Pathology of Acrocyanosis, *Brit. J. Dermat. & Syph.* 49: 100-106, 1937.

<sup>2481</sup>Simon, C. Dermatose en rapport avec des troubles du système nerveux. *Nouvelle pratique dermatologique* vol. 8 Paris 1935, Masson & Cie pp 749-807.

<sup>2482</sup>Pyramowski F. Il dermographismo nelle psicosi. *Cervello* 11: 40-46, 1932. *Ibid.* 42: 83.

<sup>2483</sup>Wigert V. Katatonie and Melanoderma, *Acta psychiat.* (Copenhagen) 2: 84-144 1976; *Ibid.* 23: 218.

edema malformations nevi hemihypertrophy<sup>286</sup> and scars from biting the hands and wrists<sup>287</sup> have frequently been recorded but the statistics are controversial and<sup>279,288</sup> some lack sufficient controls. Mumford and Chevens<sup>279</sup> emphasize the juvenile character of the skin in mentally retarded adults.

The dryness of the skin and hair the tendency to eczematous eruptions the large protruding tongue malformations of the ears, epicanthus and mongol spots<sup>289</sup> are the well known external signs of *mongoloid idiotism*. Familial xeroderma pigmentosum may be associated with severe retardation.<sup>290</sup>

### Psychogenic Dermatoses

A great number of *cutaneous reactions to psychic stimuli* are known. One has to assume that the autonomic system mediates the psychic impulses to the effector organs in the skin by the liberation of acetylcholin or sympathin (See autonomic system). Pallor blushing perspiration gooseflesh and the gray ing of the hair are proverbial phenomena caused by fear shame rage embarrassment excitement, worry and other psychic factors. Certain sensations in the skin like spine tingling shuddering itching and hair raising may also be produced by merely psychic causes, e.g. reading an exciting story fear acoustic stimuli as sour notes and shrill sounds or the touching of certain materials like silk cardboard and rough wood. Using laboratory methods very sensitive responses can be demonstrated. Not only actual sensations but even the mere imagination of a sensation like pain reduces the electric resistance of the skin in a typical way which is demonstrable by Tarchanoff's psycho-galvanic reflex. This accurately measurable drop in electrical resistance is due to the sympathetic stimulation of the sweat glands.<sup>291</sup>

The skin temperature depends on the arterial tonus which responds readily to psychic stimuli. A local temperature increase of 0.2 centigrade can be caused by mental concentration on a spot.<sup>292</sup> The famous lie-detector is based on such psychogenic reactions in the skin and other organs. It is not difficult to conceive that inflammatory processes, which are so intimately related to vasodilation may in some instances be produced by psychic causes. Many experiments have proved the truth of this assumption. There are many clinical observations which support the *psychogenic etiology of some dermatoses* but it is more often true that psychic stimuli enhance or impair an existing dermatosis than that they actually cause it. The experimental methods do not try to explain the psychic part of the sequence emotion—somatic changes. They concentrate on the latter part. The greatest attempt not to explain or to locate the psyche

<sup>286</sup>Waldenfeld E O. Congenital Hypertrophy of Left Shoulder Girdle Arm, and Hand With Nerve and Vascular Lesions. *Am J M Sc* 37: 368-373, 1930.

<sup>287</sup>Battersworth Th and Wilson, M J. Incidence of Diseases of the Skin in Feebleminded Persons. *Arch Dermat Syph* 33: 203-209, 1930.

<sup>288</sup>Harris, N. H. M. Stigmata of Degeneration in Relation to Mental Deficiency. *Proc. Roy Soc. Med* 24: 413-425, 1931.

<sup>289</sup>Brachfeld T. Mongolism. *Brit J Child Dis* 21: 341-359, 1924.

<sup>290</sup>De Sanctis C and Caccione A. L'Idiote xeroderma. *Riv sper di Dermat* 54: 369-372, 1932, 374, 43.

<sup>291</sup>Derog H. Psychische Beeinflussung der Hauttemperatur. *Journ. f. Psychol. Neurol.* 27: 209-221, 1923.

but to permit a glimpse of its mechanisms has been made by Freud and his psychoanalytic school

According to this doctrine the powerful source of psychic energy the mystic Id makes contact with somatic processes somewhere in the form of instincts. A resistance is set up against the demands of the instincts (Freud after Hinze and Shatzky<sup>2992</sup>) This leads to conflicts because the suppressed or repressed instincts are not deprived of their power They continue to seek discharge comparable to potential energy which tends to transform itself into kinetic energy Somatic processes including disease may be one of the forms of transformation In this way conflicts may lead to disease The term psychodermatosis seems appropriate for dermatoses of psychogenic origin

The case material illustrating the psychogenesis of dermatoses is large but not always conclusive Small numbers the fluctuating course of the dermatosis in question and accompanying dermatological treatment often obscure the evidence which is supposed to prove psychogenesis But in spite of these limitations the existence of psychogenous dermatoses and the value of psychotherapy cannot be denied<sup>2997,2998-2999</sup>

**Vascula: Phenomena**—Psychogenic *erythema* as an expression of modest embarrassment or excitement is usually restricted to the face and neck. About the neck or upper chest it may assume a blotchy pattern especially in women who generally are much more likely to blush than men Children of both sexes seem to blush equally with various emotions especially with guilt on telling a lie Emotional erythema has been seen in atypical sites to which the mind of the patient had been concentrated A patient blushed emotionally around a tuberculous sinus of long standing<sup>2992</sup> A woman who is examined gynecologically for the first time may show emotional erythema on her abdomen<sup>2992,2998,2999</sup>

<sup>2992</sup>The word neurodermatosis should be restricted to the dermatoses of organic diseases of the nervous system The word neurosis is often being used for relatively minor disorder of the psychic constitution which is not psychosis

<sup>2992</sup>Hinze L E and Shatzky J Psychiatric Dictionary New York, 1940 Oxford University Press

<sup>2993</sup>Bach, W T Psyche and Haut, Handb d H : Gk 4, 2 1203-1492, 1933.

<sup>2994</sup>Ginsberg, R D Psychological Aspects of Skin Diseases, Brit. J Dermat 86 116 1938

<sup>2995</sup>Altr J K Ueber Psychogenese von Hautkrankheiten, Zbl 23 132.

<sup>2996</sup>Klander J V Psychogenic Aspects of Diseases of the Skin, Arch Dermat & Syph. 36 231 232 1924.

<sup>2997</sup>MacKee G H Neurotic Eruptions, Arch Dermat & Syph 1 255, 1920

<sup>2998</sup>Warther J Die neurotischen und hysterischen Dermatosen, Dermat Wochschr 1933 I 461-470, 813-818.

<sup>2999</sup>Tracy W A and Secor F E Excoriations Cases, Arch Dermat & Syph 1 270 1920.

<sup>3000</sup>Michelson, H H The Motivation of Self-Induced Eruptions Arch Dermat. & Syph. 81: 245-250, 1915.

<sup>3001</sup>Obermayer M E Functional Factors in Common Dermatoses, J A M A 122: 842, 1943.

<sup>3002</sup>Lynch, F W Hinckley R G and Gowen, D W Psychobiologic Studies of Patients With Atopic Eczema, Arch. Dermat & Syph. 51 281-300, 1945.

<sup>3003</sup>Van de Kerk, J M and Becker S W Functional Studies in Patients With Neurodermatosis, J.A.M.A. 106 1093, 1935.

Blushing and fear of embarrassing blushing can sometimes be traced to early sexual emotions. The psychoanalysts found an underlying Oedipus complex in some pronounced cases.<sup>294</sup>

Psychogenic hemorrhages may be caused by a gruesome sight<sup>295</sup> or similar experiences. Schindler<sup>296</sup> who has devoted a monograph to the subject of spontaneous neurogenic and psychogenic hemorrhages, saw the purpuric spots most often on the lower legs of hysterical persons.

He describes three cases which were cured by hypnosis or psychotherapy. The purpuric lesions could be provoked by hypnotic suggestion.<sup>294</sup> Kohnstamm could inhibit bleeding from needle pricks by the hypnotic suggestion that the pricked left index finger would not bleed. The pricked index finger of the right hand for which normal conditions had been suggested bled in the usual manner.<sup>294</sup>

**Mystic Stigmatization**—In this connection the phenomenon of *stigmatization* has to be mentioned. The term is derived from the sixth chapter of the Epistle to the Galatians in which the Apostle Paulus says I wear the mark (stigmata) of the wounds of Jesus on my body.<sup>296,298,297</sup> Thus it means the appearance of skin lesions resembling the wounds suffered by Jesus during the crucifixion.

The numbers of more or less well acknowledged cases vary from 80 to 321 according to various Catholic sources.<sup>298</sup> The Catholic church has, at least in modern times, exercised great skepticism in this matter. The most famous and if Saint Paul's word is not taken literally probably the first of the stigmatized was Saint Francis. Sixty-two have been beatified or canonized. A medical report of an eighteenth century case of stigmatization including autopsy has recently been made accessible.<sup>293</sup> Twenty-nine cases occurred in the nineteenth century and at least three have been observed by trained modern scientists. The last case was that of the still living Theresa Neumann of Konnersreuth in the Bavarian Palatinate. The case probably resembled earlier observations in many respects.<sup>296,297</sup> Ewald<sup>299</sup> professor of psychiatry at the University of Erlangen who observed Theresa and furnished a now famous expert opinion for the physician of the bishop of Regensburg saw nickel-sized dry scab covered hemorrhagic and tender lesions on the dorsa of the hands and feet. The scabs developed from blood which oozed through the thin epidermal membrane during the ecstasies. There were smaller lesions on the corresponding spots of the palms and soles, and over the heart next to the sternum. The latter the so-called chest wound had a slightly raised edematous appearance.

<sup>294</sup>Kerker, J. A Symposium on Psychogenic Dermatoses, *Dermat. Wchnschr.* 94: 30, 1922.

<sup>295</sup>Jakobi, W. Die Stigmatisierten. Beiträge zur Psychologie der Mystik. Grenzfragen d. Nerven Seelenlebens, No. 11 pp 1-87 München, 1922, J. F. Bergmann.

<sup>296</sup>Schultz, J. H. Stigmatization, *Deutsche med. Wchnschr.* 52: 1644-1646, 1927.

<sup>297</sup>Almeida, M. Les stigmates cutanés des mystiques, *Bull. méd. Paris* 67: 667-671, 1922.

<sup>298</sup>Ewald, G. Die Stigmatisierte von Konnersreuth, *Untersuchungsberichte und gerichtliche Stenographien*, München. med. Wchnschr. 74: 1961-1992, 1927.

The American dermatologist Klauder<sup>1909</sup> who examined Theresa nine years after Ewald<sup>1903</sup> found a remarkably square dry glazed hemorrhagic lesion without any inflammation ulceration or destruction. The clot seemed in the skin rather than on it. Klauder<sup>1909</sup> also saw sharply outlined pear shaped, congestive areas 0.5 cm. long on the forehead. These stigmata which symbolized the wounds from the crown of thorns, did not have crusts.



Fig 365—St. Francis receiving the stigmata. (Painting by Francisco de Zurbarán. With permission of the Musée d. Louvre, Paris.)

On Friday Theresa went into a state of ecstasy in which she seemed to endure or witness the crucifixion of Christ. During her ecstasy the stigmata became redder. The marks did not heal in the interval. In the scant secretion of the thoracic stigma and in the tears blood was found microscopically. According to reports which Ewald could not verify and the objective truth of which he could not believe Theresa did not eat more than a quarter loaf with 3 c.c. of water daily. There were no stools but small quantities of urine containing

<sup>1909</sup>Klauder J. V., Stigmatization, Arch. Dermat. & Syph. 37: 630-636 1933.

acetone, were secreted. The girl lost nine pounds during the ecstasy but regained her weight during the interval in spite of doing house work and other activities. Ewald and other medical observers<sup>2200</sup> arrived at the opinion that Theresa's stigmata were genuine, and not artificially produced.

The psychiatric diagnosis made not only from the ecstasies but from many other preceding manifestations, was severe hysteria.

**Allergic Phenomena.**—Purely psychogenic urticaria is rare<sup>2242,2243,2244</sup> Psychic factors however were noticeable in 18 per cent of 170 cases<sup>2245</sup> of urticaria and angioneurotic edema. Stokes, Kulchar and Pillsbury<sup>2246</sup> in a thorough study of 100 cases, estimate that psychogenous influences are the sole cause of urticaria in 12 per cent and a contributory cause in 68 per cent. The urticariogenic, psychogenous background seems to be in a personality type rather than in external impinging circumstances<sup>2247,2248,2249</sup>. Allergic urticaria may result in a conditioned reflex and persist long after the exposure to the excitement has ceased.<sup>2250,2251</sup> Hebra described the case of a woman who developed urticaria by the mere thought of some urticariogenic substances (Veidsen in discussion to Kohnstamm and Pinner<sup>2252</sup>).

In a well observed case<sup>2253</sup> of suspected allergy to quinine urticaria could be produced by hypnotic suggestion of taking quinine, and quinine could be taken in hypnosis without producing urticaria if it was suggested that it was not quinine. Kohnstamm<sup>2254</sup> performed the following experiment in the presence of a group of neurologists. A cross was drawn with a pencil on both arms of a subject under hypnosis. The suggestion was given that on the left side an urticarial wheal would develop within two hours whereas the right side would remain unaltered. After about an hour under supervision the wheal formation on the left side began. Urticaria factitia was excluded.

Some patients develop urticaria on excitement. Some are able to produce wheals in a certain spot by mental concentration on this area.<sup>2255,2256</sup> Urticaria after coitus probably belongs to this group.<sup>2257,2258</sup> Dermographism is supposed to be common in neurotic patients.<sup>2259</sup> The cholinergic character of emotional urticaria has been thoroughly investigated. Rothman<sup>2260</sup> considers this condition

<sup>2200</sup>Drake, J. A. Urticaria Evoked by Emotion, *Br. J. Dermat.* 42: 164-165 1923.

<sup>2242</sup>Desbar, E. F. Physical and Mental Relationship in Hysteria, *Am. J. Psychiat.* 91: 641-662, 1934.

<sup>2243</sup>Jarcho, E. Samherard. Life of Maria Caterina Brouil. *Bull. Hist. Med.* 18: 403-419 1944.

<sup>2244</sup>Fink, A. I. and Gay, L. W. Review of 70 Cases of Urticaria and Angioneurotic Edema, *J. Allergy* 3: 618, 1934; also *Bull. Johns Hopkins Hosp.* 38: 380-392, 1934.

<sup>2245</sup>Stokes, J. H. Kulchar, M. V. and Pillsbury, D. M. Effect on the Skin of Emotional and Nervous States. (Urticaria) *Arch. Dermat. & Syph.* 51: 470-498 1925.

<sup>2246</sup>Stokes, J. H. The Personality Factor in Psychoneurotic Reactions of the Skin, *Arch. Dermat. & Syph.* 43: 780-801 1940.

<sup>2247</sup>Blumenfeld, W. Treatment in Peripheral Vascular Disease, *Arch. Phys. Therapy* 21: 267-269 1940.

<sup>2248</sup>Sack, W. Zum Mechanismus der psychophysischen Schaltung. *Nervenztr.* 6: 87-92, 1923.

<sup>2249</sup>Kohnstamm, O. and Pinner, M. Blasenbildung durch hypnotische Suggestionen, *Arch. f. Dermat. u. Syph.* 91: 378-380 1928.

<sup>2250</sup>Karlsmann, A. J. Ueber d. Wesen der psychischen Urticaria, *Arch. f. Dermat. u. Syph.* 173: 431-436, 1926.

<sup>2251</sup>Kohnstamm, O. Demonstration Deutsche Naturf. Versam. 43: 447-448, 1911 1912.

<sup>2252</sup>Hirschfeld, M. *Semipathologie*, vol. 3, Bonn, 1922. A. Staras and E. Weber p. 84.

<sup>2253</sup>Wengraf, F. Eine Dermatoze post coitum, *Psychother. Praxis* 3: 80-82, 1924.



as one of the rare cases of allergy to a physiological metabolic product namely acetylcholin Rothman<sup>394</sup> has in two out of three cases successfully desensitized patients with emotional urticaria by gradually increasing intradermal doses of acetylcholin.

Many allergic phenomena like urticaria asthma and hay fever are highly subject to psychic influence. There is much evidence accumulated that certain types of character namely the driving high-strung subtle intelligent, ambitious sensitive also the imbalanced and maladjusted predispose to allergy.<sup>395</sup> Worry grief anxiety fatigue stress and strains, unsatisfied longing for love and affection may increase specific allergic reactions and prevent their healing.<sup>396</sup> Experimental allergic wheals in persons with pronounced allergy can be increased or inhibited by hypnotic suggestions.<sup>397,398</sup>

**Other Psychogenic Dermadromes—Sweating—**Mental stimuli, e.g. mental efforts in solving an arithmetical problem pain or excitement, may in some persons evoke sudden frontal axillary and especially palmar sweating.<sup>399,400,401,402</sup> Apprehension of having a wet hand when shaking hands may cause palmar perspiration.

The sweat secretion generally but especially that of the palms and soles is a sensitive somatic receptor of psychic stimuli.<sup>403</sup> This is best demonstrated by Tarchanoff's psychogalvanic reflex (see above) which indicates increased perspiration by lowered electric resistance of the skin. The shouting of words to the test person is sufficient to evoke the reflex. *Dysidrosis* is in some cases quite subject to psychogenic factors.

*Psychogenic blisters* represent a more severe reaction than the changes which have been mentioned so far. The blisters may even be followed by necrosis. While great skepticism prevails with regard to the so-called pemphigus hystericus of the older authors,<sup>404</sup> it cannot be doubted that bullae can be produced by hypnotic suggestion of a burn.<sup>405,406,407,408</sup> Kreibich and Doswald<sup>409</sup> hypnotized a physician and touched him with a stick of wood suggesting that he was being burnt with a match. After three minutes an erythema the size of a match head appeared and after three more minutes a blister of the same size was visible. Biopsy after 24 hours revealed changes identical with that of a third degree burn.<sup>410</sup>

Similar experiments have been repeated by many authors and with precautions which ought to rule out fakery including a plaster of Paris dressing during the experiment.

<sup>394</sup>Rothman, J. H. and Beerman, H. Psychosomatic Correlations in Allergic Conditions. Problems and Literature, Psychosom. Med. 2: 433-456, 1940.

<sup>395</sup>Diehl, F. and Heinichen, W. Psychische Beeinflussung allergischer Reaktionen, Munchen. med. Wochenschr. 78: 1003-009 1931.

<sup>396</sup>Alarcón, H. and Sahlgren, E. Untersuchungen über die Einwirkung der hypnothetischen Suggestion auf die Funktionen des vegetativen Systems. Acta psychiat. et neurol. 11: 119-136, 1930.

<sup>397</sup>Kase, Y. Physiology of Human Perspiration. London, 1934, J. & A. Churchill Ltd.

<sup>398</sup>Kosaka, T. Demonstration of Psychical Sweating by Means of Milner's Method, Jap. J. med. Sci. Trans. 111 Biophysics 2: 2, 1931. Ebl. 63: 303.

<sup>399</sup>Onofreia, P. Ipoerichidasi infantiului universal si insuficienta psihică, Revue de studi psihic. 19: 421-443, 1939.

<sup>400</sup>Kreibich, K. and Doswald, H. C. Posthypnotische Hautphänomene, Monatsh. f. prakt. Dermat. 43: 634-640 1900.

*Herpes simplex* and especially *herpes genitalis* is subject to psychogenic influences, such as guilt and fear of venereal infection after extramarital coitus.

*Pruritus* is highly susceptible to psychogenic influences.<sup>292b</sup> Every dermatologist knows of patients with lichen ruber and lichen Vidal chronic eczema ~~poorana~~ and prurigo whose skin disease is more itchy on excitement and calms down when the patient does. However while mental impulses are very common contributory factors purely psychogenic pruritus is rare.<sup>292a, 292b</sup>

In order to prove the existence of completely psychogenic pruritus, Sack reduced pruritus by hypnotic suggestion in the locally anesthetized finger of a patient. Pruritus may be a symptom in endogenous and reactive depressions.

The sexual background of anal and vulvar pruritus has frequently been analyzed.<sup>294, 295</sup> Many psychoanalysts believe that the pruritic seizures and the relief of tension achieved by violent scratching are sexual or homosexual equivalents. These relations seem to have been overemphasized.<sup>295</sup>

*Psychogenic eczema* is illustrated by the following case.<sup>292c</sup> Psychoanalysis traced the origin of an eczema on the buttocks to a nauseating dream in which the patient had seen himself covered with feces as high as the eczema indicated. Psychoanalysis cured the patient.<sup>292b, 292c</sup>

*Sudden bleaching of the hair* caused by terrifying experiences is still controversial. The two leading American textbooks of dermatology arrive at opposite opinions. Ormaby and Montgomery<sup>293</sup> admit it as a rare probability of clinical experience while Sutton and Sutton<sup>297</sup> explain it as the result of the removal of cosmetic coloration or of the application of a bleach. The main argument against it is the lack of greater numbers of observation in both World Wars with millions of terrifying occasions. The number of well documented cases<sup>294</sup> seems too small to rule out the possible errors, especially that of having been gray before the event.<sup>292c</sup> The physiological possibility of a sudden graying must be admitted. Landolt's old theory that in such cases the pigment is hidden by reflecting gas bubbles has found considerable supporting evidence.<sup>294</sup>

Mental stress, strain and shock, probably play an important role as a trigger factor in *alopecia areata*.<sup>292b</sup>

In the opinion of the *psychoanalysis* psychogenic dermatoses always have a meaning.<sup>292b</sup> In some instances they symbolize their origin as in the case of ecchymoses after seeing blood<sup>296</sup> in the mystic stigmas, or in the cases of *peoriasis* provoked by the terrifying and prolonged sight of decomposing corpses in

<sup>292a</sup>Pearson, G. H. J. Some Psychological Aspects of Inflammatory Skin Lesions, *Psychosomat. Med.* 2: 22-23, 1940.

<sup>292b</sup>Kasper, J. V. Psychogenic Aspects of Skin Diseases, *J. Nerv. Dis.* 84: 249-272, 1936.

<sup>292c</sup>Bruckenkeller, A. Psychogene (onkogene) Krankheitsbilder. *Arch. f. Kinderh.* 96: 51-55, 1922.

<sup>293</sup>Rogerson, G. H. Psychological Factors in Skin Diseases, *Practitioner* 162: 17-25, 1936.

<sup>294</sup>Vigoda-Lestai, G. Ossicle precoci palcapite di guerra, *Foliculosis* (nat. prat.) 23: 680, 1916.

<sup>295</sup>Ingram, J. T. Baldness, Causes and Treatment, *Bl. Press* 296: 41-42, 1942.

<sup>296</sup>Schädel, F. Psychophysiologie of the Skin, *Arch. Dermat. & Syph.* 96: 512-514, 1921.

front of trenches where the patient fought.<sup>307,308</sup> In some of these cases cure has been accomplished by hypnotic suggestion. Schilder<sup>309</sup> expresses the opinion without proving it that anal itching is an expression of sadomasochistic tendencies, blushing manifests a narcissistic attitude and blisters and hemorrhages are closely related to a hysteriform attitude with a strong infantile Oedipus complex.

While classic psychoanalysis has found but little acclaim among the dermatologists, the importance of tensions, conflicts, emotions, overwork, fatigue, shock, worries, insomnia, inferiorities, frustrations, and other psychic factors on the origin and course of dermatoses has been emphasized time and again.

This has been done in the most human, practical and convincing way by Stokes.<sup>310</sup> Purely psychogenic dermatoses are rare and do not develop typical morphological pictures with the exception of the self-inflicted dermatoses.

Yet it is exceedingly common that the psyche influences the course of a disease for better or worse. *psoriasis*, *lichen planus*,<sup>311</sup> chronic *eczema*, *lichen Vidal*, *dermatitis herpetiformis* and *slopecia areata* furnish the best examples (see also Obermeyer<sup>312</sup>). The psychosomatic relationship of *atopic dermatitis* is particularly striking.<sup>305</sup> These patients are often highly intelligent, aggressive and ambitious, as well as tense and fidgety. It is more likely that their nervousness is primary rather than due to their itching and disfigurement which of course may also leave its mark. Their behaviour and character are quite different from other suffering or disfigured people. Family conflicts are often in the background of such cases, not infrequently caused by arguments on the treatment or diet. This was strikingly illustrated in one of the author's cases. An intelligent boy of 13 with severe atopic *eczema* improved immediately after the mother was advised to discontinue all discussions and arguments on his diet which had disturbed almost every meal. Later the trouble recurred on other conflicts. Overattention as an only child, or resentment because of sibling rivalry, frustration and parental rejection may also occasionally express themselves in more intensive itching and scratching and consequent impairment. The children soon learn to use their ailment as a weapon.<sup>313,314</sup>

In this group probably belongs *acne urticata*.<sup>315</sup> In this condition the lesions, which may occur on the face or anywhere on the body, are at first wheals or papules which itch intensely and become infiltrated and excoriated under constant scratching. They disappear after several weeks leaving a pigmented spot. The eruptions may keep appearing for years. In some of these cases a psychogenic background is obvious. In one of the author's cases the disease broke out in a young woman after the husband had gone overseas and eased up on the news

<sup>307</sup>Bergmann, O. Psychogenese von Hautsymptomen. *Stettin f. d. ges. Neurol. u. Psychiat.* 96: 589-600, 1923.

<sup>308</sup>Bergmann, O. Ueber psychogene Hautveränderungen. *Psychotherapeut. Prax.* 1: 23-36, 1924.

<sup>309</sup>Schilder, J. H. Functional Neuroses as Complications of Organic Diseases: A Office Technical Approach. *WMA Spec. Reference to the Neurodermatoses*, J. A. M. A. 106: 1007-1012, 1933.

<sup>310</sup>Gecklerman, W. R. The Relationship of Emotions and Cutaneous Lesions. *Med. Clin. North America* 18: 845-849, 1930.

<sup>311</sup>Rogerson, C. H. Psychotherapy and the Asthma-Eczema-Prurigo Complex in Children. *Brit. J. Dermatol.* 45: 368-378, 1954.

<sup>312</sup>Kaplan, M. Ueber einige ungewöhnliche Formen von Acne (Folliculitis). *Arch. f. Dermat. u. Syph.* 20: 87-96, 1904.

that he was out of the danger zone. The patient was an intelligent high-strung person of a type commonly encountered in atopic dermatitis to which the condition seems to be related. Acne urticata also may be seen in atopic dermatitis.

*Burning tongue* is highly susceptible to psychic influence. In this condition the impulse may act through the sensitive psychosomatic mechanism of the gastric acidity. Becker and Obermayer<sup>1943</sup> call *neuronychia* nail changes which either consist of separation of the nail from the bed or of superficial pitting, thickening, thinning or splitting. The authors saw the condition associated with neurodermatitis or as the only somatic manifestation of nervous instability and exhaustion.

**Hysteria**—Conscious or subconscious production of symptoms, the main feature of hysteria, leads into the field of the self-inflicted dermatoses (neurotic excoriations, dermatitis factitia). The variations of clinical appearance are innumerable but there are some features which are often encountered. The feigned



FIG. 360.—Acne excoriat. The scarring is caused by ultraviolet light.

lesions are usually within the reach of hands, preferably of the right hand. The artefacts and their scars often have a strange angular, round or linear "unnatural" appearance which arouses the suspicion of the experienced dermatologist.<sup>1944</sup> Sometimes traces of a chemical used in the production of lesions can be found in the surroundings or on the scab. If the circumstances permit the application of a sealed occlusive dressing especially with plaster of Paris is advisable. If healing of the suspected lesions of long standing follows, further evidence of self-infliction is given.

<sup>1943</sup>Becker S. W. and Obermayer M. E. *Modern Dermatology and Syphilology* Philadelphia, 1943, J. B. Lippincott Co.

<sup>1944</sup>Thompson F. E. and Shiffman H. Neurotic Excoriations, *Arch. Dermat. & Syph.* 46: 534-535, 1942.

However one should keep in mind that the typical pathomimic changes represent only a minority among the great variety of entirely or partially self inflicted lesions. More commonly a spontaneous dermatosis like acne or a patch of eczema is kept going by picking scratching or treating. Excoriated acne is found not only in young girls (Brocq's *acné excorié des jeunes filles*) but also in middle aged women.

The psychology of self induced eruptions<sup>1883, 2034, 2097, 2360, 2403</sup> ranges from the sometimes criminal but simple and mentally normal cases of military or civilian malingering to more complicated and often decidedly pathological states of mind. In one of these cases (Dieulafoy after Simon<sup>2103</sup>) recurrent deep ulcerations of the hands and arms led to various major operations and finally to the amputation of one arm. The patient would not have hesitated to have his other arm amputated if the right diagnosis had not been made. Under some grilling the patient admitted that he had placed pieces of potassium hydroxide on the



Fig 267 Trichostillomata.

mantlepiece and then put his arm on it. Similar cases are on record. The most plausible motivation is an escape into disease. The suffering arouses sympathy and attention which the patient is craving. Strangely enough the motivation may also be lack of erotic attention. A woman may try to get the sympathy and with it the love of her husband. This might be called the poor little dear motivation. Psychoanalysis may also detect underlying unconscious motives



Fig. 363.—Trichotillomania.



Fig. 360.—Trichotillomania. (Courtesy Division of Dermatology Department of Medicine University of Chicago.)

of guilt and punishment<sup>2900,2946</sup> In this group belong the patients who keep pyodermic lesions on the face open with tweezers.

Some of these patients are *feeble-minded* who without any purpose follow an exaggerated urge to remove all little follicular plugs, to dig after or pull out 'ingrown hairs' and to scratch every scale on the scalp.

The cases of neurotic excoriations lead to the true cutaneous *manias and phobias*. There is the urge to rub the hair between the fingers, to bite the nails to break hairs or to pull the hair out (trichotillomania). This latter condition



Fig. 270.—Neurotic excoriations.

usually found in children is often combined with anomalies like enuresis and mental retardation<sup>2946,2947</sup> paranoia<sup>2948</sup> or postencephalitic state<sup>2949</sup>. It has also been observed as a psychic epidemic in institutions (Haldin Davis in discussion to O Donovan<sup>2944</sup>). Transitory cases without apparent deeper significance are also known<sup>2951</sup>. Apparently unique is a case of plucking the mustache.<sup>2952</sup>

<sup>2900</sup>Casassa, N. Sull'importanza di fattori psichici in dermatologia ( proposito di astelesioni cutanee in isteriche) Boll. d. Soc. med-chir. Pavia 48: 115-162, 1930. Ed. 35: 261.

<sup>2940</sup>Dohl, S. Ueber Trichotillomanie. Dermat. Wochschr. 86: 236-239, 1930.

<sup>2941</sup>Tarszsi, O. L. Sz. di un caso di Trichotillomania. Peditria prat. 10: 282-407, 1922.

<sup>2942</sup>Chasaki, K. Ein Fall von Trichotillomania, Jap. J. Dermat. 22: 70, 1932. Ed. 42: 612.

<sup>2943</sup>Perantoni-Satta, O. Considerazioni cliniche su un caso di parodotricotillomania, Dermosinlografo 6: 449-460, 1931.

<sup>2944</sup>O Donovan, W. J. Infantile Trichotillomania, Proc. Roy. Soc. Med. 26: 826-828, 1932.

<sup>2945</sup>Playter, A. Hair Plucking, Am. J. Dis. Child. 51: 326-337, 1936.

<sup>2946</sup>Photinos, P. B. Aetiology der Trichotillomanie. Dermat. Wochschr. 61: 229-240, 1921.

Cutaneous phobias and *hypochondriac complaints* which appear suddenly should be reason to search for an underlying psychosis<sup>272,288</sup> or addiction to morphine or cocaine.

Patients who persistently bring little follicular plugs, scales, or woolen fibers wrapped in paper or kept in a box to convince the doctor that they have worms or insects in their skin that they feel them creeping, clicking, digging and that they have to crush them between their fingers, have delusions and belong to a psychiatrist.<sup>284-286</sup> Such delusions of parasites or dermatozoa may occur in the toxic psychoses, in dementia praecox, in involutional melancholia, and in paranoia and paranoid conditions. The prognosis is poor. Only about 10 per cent of the reported 51 cases have been cured.<sup>286</sup> A greater significance may be attached to the severe cases of patients who wash their hands excessively, avoid touching a door handle and have constant fear of body odor or of being dirty or of blushing.



Fig. 371 —Neurotic nail biting.

*Tattooing*, while normally a badge of membership to certain groups (sailors) or just being a fad, may also express psychopathological conditions<sup>289,290</sup> with an erotic homosexual or criminal background. During the second World War the rejection rate for tattooed men was almost 50 per cent greater than for nontattooed men, and 58 per cent of all rejections among tattooed men were on the basis of neuropsychiatric disability, in contrast to only 38 per cent among the nontattooed.<sup>291</sup> These military statistics are according to the authors,

<sup>289</sup>Graham-Little E. Neurotic Excitations. *Proc Roy Soc Med* 26: 676, 1931.

<sup>290</sup>Ekbom K A. Prävalenz Dermatosenkrankh. *Acta psychiat et neurol* 12: 227-230, 1933.

<sup>291</sup>Wilson J W and Miller H E. Delusion of Parasitosis (Scrophobia). *Arch Dermat & Syph* 54: 29-37, 1946.

<sup>292</sup>Wright O B. Psychosomatic Aspects of Dermatoses. *Clinics* 111: 711-727, 1944.

<sup>293</sup>Dreschberg W. Psychologic Motives in Tattooing. *Arch Dermat & Syph* 59: 5-602, 1934.

<sup>294</sup>Perry A. T. (New York, 1933) Simon & Schuster Inc.

<sup>295</sup>Loefer J and Kohn H M. Tattooing Among Soldiers. *Psychiatric (Signal Corps) Am J Psychiat*, 1947: 326-327, 1943.



based on numbers large enough to be valid though exact absolute figures are not given. Among the men rejected for antisocial inclinations 68 per cent had multiple tattoos.

*Psychotherapy of Dermatoses*—If a psychic factor causes or as it more frequently happens influences the course of a skin disease the removal of this cause should be tried. The office technique approach<sup>790,791</sup> may be learned depending on the interest and aptitude of the dermatologist but at the present stage of our training the aid of a trained psychiatrist should be sought<sup>792,793</sup> to the greater advantage of both parties.

*Hypnosis* has occasionally been successful in the treatment of psoriasis<sup>794</sup> and eczema<sup>795</sup>.

The *psychotherapy of juvenile as well as ordinary warts* has been practiced by lay healers for centuries under many forms<sup>796</sup>. Bloch<sup>797</sup> stimulated scientific interest in the matter by healing 44 per cent of verrucae vulgares and 88 per cent of verrucae planae by verbal suggestion painting with color and turning on a buzzing electric motor. No consensus exists about the post hoc ergo propter hoc but it is the impression of many experienced dermatologists that suggestion therapy is effective in a varying percentage. Some cases are very impressive<sup>798,799</sup>. Memmesheimer and Eisenlohr<sup>798</sup> treated 70 out of 140 cases of ordinary warts by suggestion and left the other 70 untreated. There was no significant difference in the percentage of cures. The cure of condylomata acuminata by suggestion has been reported by Bonjour<sup>797</sup>.

<sup>790</sup> Weiss, M. and English, O. S. *Psychosomatic Medicine* Philadelphia, 1915 W. B. Saunders Co.

<sup>791</sup> Wlach, J. M. A. *Heilung der Hypnose bei Psoriasis*, Dermat. Wchnschr. 190 231-236, 1933.

<sup>792</sup> Dabnikov E. *Die Frage der Behandlung des Ekzems nervösen Ursprunges durch Hypnotismus*, Vrach. delo 18 634-636, 1933 Ed. 68 470.

<sup>793</sup> Ick, A. G. *Hypnotism of Warts Disappearing Without Topical Medication*, Arch. Dermat. & Syph. 38 506-531 1937.

<sup>794</sup> Bloch, B. *Ueber die Heilung der Warzen durch Suggestion*, Klin. Wchnschr. 8 2371-2380, 1927.

<sup>795</sup> Dobl, R. *Heilung der Warzen durch Suggestion*, Jap. J. Dermat. 30 33, 1930 Ed. 36: 318.

<sup>796</sup> Memmesheimer A. M. and Eisenlohr E. *Suggestivbehandlung der Warzen*, Dermat. Wchnschr. 62: 63-68, 1931.

<sup>797</sup> Bonjour J. *La guérison des condylomes par la suggestion*, Presse méd. 30 61-67 1929.

## CHAPTER XLI

### DISORDERS OF THE GASTROINTESTINAL TRACT

The various sections of the gastrointestinal tract are highly interdependent. Gastric hyperacidity for example may lead to increased motility of the small intestine causing the chyme to be rushed to the colon before the digestion in the bowel is completed. Thus toxic intermediate products may be reabsorbed and transported through the portal system to the liver where detoxification may take place provided the liver functions are unimpaired. A fraction however may enter the circulation directly through the vena cava. Deficiency of the antiseptic hydrochloric acid results in incomplete digestion and partial retention of the food. Another important consequence is the change of the intestinal bacterial flora, with ensuing putrefaction of large amounts of mucus. Local inflammatory lesions may change the permeability of the mucous membranes, thus permitting the passage of toxic and allergenic substances<sup>2768-2772</sup> through the intestinal barrier though much work remains to be done to prove the pathogenesis of skin changes by pathological absorption.

**Dermadromes.**—Yet cutaneous symptoms arise only in a small fraction of gastrointestinal disorders. No obligatory dermadrome is known in connection with gastrointestinal diseases but several dermatoses occur occasionally. The percentage of skin diseases in large series of gastrointestinal cases is small. Even the conditions commonly ascribed to gastrointestinal causes, such as pruritus, urticaria and eczema were recorded in less than one per cent of 5000 different gastrointestinal cases.<sup>2773</sup> Among 595 gastrointestinal cases<sup>2774</sup> rosacea was observed in 3.5 per cent.<sup>2775</sup> In some groups, e.g. peptic ulcer or colitis, the incidence of dermatoses is higher. The percentages of varied gastrointestinal disorders in patients suffering from chronic eczema, neurodermatitis, urticaria, pruritus, acne, rosacea and acne urticata are significant. The possibility of a gastrointestinal cause should be kept in mind in persistent and unexplained cases of these dermatoses.

**Mouth.**—While the oral cavity is very often concomitantly affected by dermatoses, or takes part in manifestations of internal disorders, a primary mouth disease only rarely causes dermadromes. In this connection one should remember the role the teeth and tonsils play in focal infections. Perléche may be caused by malocclusion and ill fitting or old dentures and salivation.<sup>2776</sup>

<sup>2768</sup>Urbach, E. Stagen-Darmtrakt und Haut, Wien, med. Wchnschr. 1937 I: 298-294, 323-326.

<sup>2769</sup>Wiedinger, O. Die endogene Natur mancher Hautkrankheiten, Verh. d. Ges. f. Verd.-u. Stoffwechselkr. Vienna, pp. 94-111, 103-123, 1920. Kbl. 28: 585.

<sup>2770</sup>Wiegner, O. Verdauungsstörungen und Dermatosen, Wien, klin. Wchnschr. 29: 598-600, 1926.

<sup>2771</sup>Heander, A. The Estero-Dermal Syndrome. Urol. & Cutan. Rev. 25: 504-509, 1921.

<sup>2772</sup>Reyn, A. Rosacea, Kbl. 32: 463, 1934.

<sup>2773</sup>Koppele, N. B. Gastric Analysis in Acne Rosacea, California & West Med. 25: 118-120, 1921.

<sup>2774</sup>Freund, H. Perléche bei Erwachsenen. Interlabialzytose und ihre symptomatische Bedeutung. Arch. f. Dermat. Syph. 164: 6-637, 1932.

The shape of the lips and the tendency to form persistent wrinkles or folds at the angles of the mouth may favor localized mycotic or bacterial infection particularly in diabetics. The author saw a mother of 75 years and her son of 52 years who both had a peculiarly hanging upper lip as a familial trait suffering from almost incurable perleche. Persisting eczema of the face and cheilitis even severe papillomatous forms, may occasionally be caused by pyorrhea and oral ulcerations.<sup>2775</sup> Salivation especially during the night may well cause dermatitis which according to the sleeping habits of the patient may be unilateral<sup>1145</sup> or bilateral.

### Diseases of the Stomach

A great number of investigators have tried to correlate the status of gastric acidity with skin disease (Spiethoff<sup>2776</sup> and later also investigations of his pupils Ehrmann<sup>2777</sup> 1903 Lejhanec after Ottenstein.) The results have shown that a general tendency to lowered gastric acidity exists in pruritus<sup>2778</sup> eczema neurodermatitis<sup>2779</sup> chronic urticaria rosacea<sup>2773,2775,2780,2781</sup> seborrheic



Fig. 272 — Chronic perleche caused by ill-fitting dentures.

<sup>2775</sup>Doogen K. v. a. Zusammenhang von Krankheiten im Munde und im übrigen Körper. *Stecher f. Stomatol.* 31: 1109-1130 1934. *Abh.* 99: 102.

<sup>2776</sup>Spiethoff B. Magenstörungen bei Hautkrankheiten. *München med. Wchnschr.* 50: 991-913.

<sup>2777</sup>Ehrmann, A. Ueber den Zusammenhang zwischen Verdauungsstörungen und Dermatosen. *Wien klin. Wchnschr.* 55: 754-757 1903.

<sup>2778</sup>Ehrmann, A. Ueber den Zusammenhang der Neurodermitis mit Erkrankungen des Verdauungstraktes und Störungen der inneren Sekretion. *Arch. f. Dermat. Syph.* 128: 245-300 1923.

<sup>2779</sup>Urbach E. Röntgenologische und klinische Befunde am Magen-Darmtrakt bei Ekzemen und ihre Bedeutung für eine kausale Therapie. *Arch. f. Dermat. Syph.* 143: 39-41 1923.

<sup>2780</sup>Eastwood, S. R. Gastric Secretion and Other Digestive Factors in Rosacea. *Brit. J. Dermat.* 40: 91-104, 144-157 1923.

<sup>2781</sup>Stekow J. H. and Pillsbury D. M. Dermatoses and Gastric Diseases. *Arch. Dermat. & Syph.* 21: 903-903, 1930.

<sup>2782</sup>Wipser H. G. Magensekretionsstörung und Haut. *Dermat. Wchnschr.* 116: 317-322, 1940.

<sup>2783</sup>Brown, W. H. Smith, M. S. and M. Lachlan, A. H. Fractional Gastric Analysis I. Diseases of the Skin. 316 Cases. Special Reference to Rosacea. *Brit. J. Dermat.* 47: 181-190 1934.

dermatitis moniliformis in diabetes, kraurosis vulvae<sup>2794</sup> and some other dermatoses.<sup>2795</sup> Urbach<sup>2797</sup> and also Ehrmann<sup>2798</sup> emphasized the frequent (22 per cent) finding of hyperperistalsis along with anacidity in cases of neurodermitis.

Great and almost unexplainable discrepancies exist among the many reports<sup>2796-2798</sup> (also Johansen after Ottenstein<sup>9</sup>)

Newer investigations partly allowing for the physiological subacidity of the higher age classes,<sup>2799,2796</sup> have confirmed though not unanimously<sup>2796</sup> that the gastric acidity tends to be subnormal in chronic inflammatory dermatoses<sup>2793</sup> (Lejhanec after Ottenstein) even if the involved skin area is relatively small<sup>2792</sup>

The observations differ in the acute dermatoses and in the acute exacerbations of chronic skin diseases. Such states seem more likely to coincide with a tendency to hyperacidity. This would be in line with observations of hyperacidity after mechanical irritation radiation with ultra violet light,<sup>2790,2794</sup> X-ray<sup>2790</sup> skin irritations with mustard plaster<sup>2792</sup> and extensive burns (Diehl Jr after Urbach<sup>2792</sup>). Very severe burns however may cause anacidity (Geber after Urbach<sup>2790</sup>). The serum of blisters from burns or freezing with CO<sub>2</sub> snow contains a histamine like substance.<sup>2790</sup> It is therefore suggestive to explain the hyperacidity as the result of release of histamine from the inflamed skin<sup>2792,2793</sup>. More difficult to explain is the subacidity in a relatively small lesion. In this case skin and stomach disorders are likely to be caused by a common factor. The individual constitution also has a great influence on the acidity.<sup>2792</sup> The favorable effect of HCl therapy on some skin diseases would seem to prove that the subacidity is the cause of the skin disease. Unfortunately the value of this often recommended treatment is not generally confirmed<sup>2792</sup>

Elimination of toxic substances from the skin into the stomach may be the cause for gastric ulcers in extensive burns (Diehl J after Urbach<sup>2797</sup>) though thirty autopsy reports<sup>2794</sup> do not mention such lesions. Little can be said as to whether ulcers associated with dermatitis<sup>2794,2796</sup> are due to eczema or

<sup>2794</sup>Green, P. Non-Pustular Eruptions Due to Deficiency of Vitamin B Complex, Arch. Dermat. & Syph. 63: 504-526, 1941.

<sup>2795</sup>Arriv, S. Jr. Gastric Secretion in Pustular Eczema and Dermatitis Herpetiformis, Arch. Dermat. & Syph. 59: 454-459, 1929.

<sup>2796</sup>Waller, S. Beiträge zur Ätiologie der Ekzeme. Orvosi Hetil. 68: 111, 112, 1921. Zbl. 24: 260.

<sup>2797</sup>Diehl, J. H. and Beerbaum, H. Effect on the Skin of Emotional and Nervous States. IV. The Boomer Oculi. Arch. Dermat. & Syph. 58: 478-481, 1932.

<sup>2798</sup>Bergman, O. Keiselschmerz von Ulcus pepticum und Hautkrankheiten, Wien klin. Wochenschr. 67: 945-94, 1924.

<sup>2799</sup>Voss, H. and Voss, F. Veränderungen der Magerssekretion nicht als Ursache sondern als Folge von Hautkrankheiten an Menschen und Weibchen, 1937 II: 1, 96-144.

<sup>2790</sup>Voss, F. Relation Between Disorders of Secretion and Skin, Dermat. Wochenschr. 111: 846-847, 1946.

<sup>2791</sup>Diehl, F. Die Wirkung der Ultra violet bestrahlung der Haut auf die Magerssekretion. Masaryk-Studienberg. Arch. 189: 367-371, 931.

<sup>2792</sup>Amesio, M. Sulla modificazione della secrezione gastrica per effetto di stimolazione sulla cute della regione epigastrica. Arch. Ital. di mal. d. app. diger. 1: 44-192, 1932. Zbl. 42: 144.

<sup>2793</sup>Dumas, A. and Anselme, E. Relations entre la peau et le digestion. Verh. 9 Internat. Congr. Derm. 1: 164-16, 1933. Also 2: 22-36, 1930. Zbl. 53: 74 and 84, 1934.

<sup>2794</sup>Colebrook, L. and others. Studies of Burns and Scalds. Medical Research (Comm. 8) Serial Report Series X: 219. London, 34. His Majesty's Stationery Office.

<sup>2795</sup>Larlet-Jarab, L. Skin Diseases and Functional Disturbance of Various Organs. Procs. 2nd. 23: 1699-1702, 1923.

vice versa or whether ulcers and dermatoses have a common cause. The impression prevails that there exists a more than coincidental relationship.

The advent of *gastroscopy* has recently revealed some relations which were not known before. The gastric mucosa takes part in cutaneous lichen planus in about 20 per cent of the cases. Urticaria may show in the stomach and skin simultaneously.<sup>299,300</sup> Vesicular gastritis has been seen to accompany some cases of acute vesicular dermatitis. In stationary eczema the gastric mucosa has usually been found in normal condition. Gastritis of varying degrees of severity was present in 18 out of 19 patients with rosacea whereas among the 13 control cases of other dermatoses only 4 patients showed evidence of gastritis.<sup>299</sup> In 2 patients coincidental improvement of both gastritis and rosacea could be visualized by the gastroscope.

Urbach<sup>299</sup> suggests that the dysfunction of the gastric mucosa may lead to increased permeability for substances from incompletely digested food which normally cannot be absorbed. This may cause allergization with cutaneous symptoms like urticaria, eczema, pruritus, urticaria, papulosa etc. Abnormal absorption of allergens may also occur from gastric or duodenal ulcers.

The validity of the old observations regarding the *tongue in gastric conditions* has recently been checked by Oatway and Middleton.<sup>300</sup>

The surface of the tongue reflects the acidity of the stomach quite reliably. In *hyperchlorhydria* and also in peptic ulcer the tongue is rarely smooth but often scrotal or coated. Superficial defects may appear in the fur of the posterior tongue a lesion which has been related to gastric ulcer.<sup>300</sup> In *achlorhydria* or subacidity smoothness of the tongue is common and still more so when achlorhydria is combined with anemia. The patients often complain of soreness of the tongue and a dry throat though objective changes are frequently absent.

### The Small Intestine

Pain, distention, audible peristaltic noises, nausea, vomiting, diarrhea and constipation are the primary symptoms which characterize disorders of the small bowel (Ingelfinger in Portis<sup>301</sup>).

Besides the inspection of the stools, chemical, microscopic, bacteriological and helminthological examinations should be carried out. Enteritis without any involvement of other parts of the tract is relatively rare.

**Dermadromes**—*Pruritus*<sup>310</sup> urticaria and eczema have been frequently found to accompany enteritis. The connection was usually demonstrated by

<sup>299</sup>Overvallier P. and Moutier F. L'estomac des eczémateux, Verh. 9. Internat. Congr. Dermat. 2: 167-172, 1936. Bib. 54, 890.

<sup>300</sup>Overvallier P. and Moutier F. Les mao dans l'eczéma vulgaire à début et à prédilection antibrachiaux, N. trition 6: 10-34, 1936. Bib. 54, 893.

<sup>301</sup>Usher II. Gastroscopic Observations in Rosacea, Arch. Dermat. & Syph. 41: 251-255, 1941.

<sup>302</sup>Oatway W. R. J. and Middleton W. R. Correlation of Lingual Changes With Other Clinical Data, Arch. Int. Med. 69: 800-878, 1932.

<sup>303</sup>Gleasoner K. Ueber Ulcerosung, Arch. Verdauungskr. 81: 68-73, 1932.

<sup>304</sup>Portis, S. A. Diseases of the Digestive System, Philadelphia, 1944. Lea & Febiger.

the effect of dietary measures<sup>2895,2879,2092</sup> or intestinal treatment with activated charcoal<sup>2893</sup> after protracted topical therapy alone had failed. Protein putrefaction and carbohydrate fermentation could frequently be demonstrated in the feces in eczema especially perianal eczema, acne, urticaria, pruritus<sup>2894</sup> and in infantile eczema<sup>2895</sup>. The bacterial flora produces porphyrins, the light sensitizing property of which is well known.

Urinary indoxyl, a sign of intestinal putrefaction, was not found increased in 42 cases of eczema<sup>2896</sup>. Vaccines derived from fecal bacteria have been found useful in the treatment of some dermatoses, but this method has not found much acclaim from dermatologists. Achylia gastrica and enteritis may be followed by the accumulation of feces and mucus in the cecum with subsequent inflammation. This typical syndrome of typhilitis (cectus)<sup>2879,2897</sup> with dull pain in the ileocecal region is often mistaken for appendicitis. Neurodermatitis lichen urticatus, urticaria and eczema have quite frequently been found associated with typhlitis. These dermatoses disappeared after treatment of the typhlitis with HCl and a diet free of irritating cellulose fibers.<sup>2898,2879,2897</sup> Creosote has been advocated as an intestinal disinfectant.

**Sprue.**—Sprue is a disease of the small intestine characterized by functional motor disorders and impaired absorption of foods particularly fats (Ingelfinger in Porter<sup>2899</sup>). The cause is not known but a nutritional deficiency probably resulting from a protracted diet deficient in vitamin B complex and in proteins and too rich in carbohydrates, is suspected. Manson Behr<sup>2899</sup> emphasizes the importance of preceding intestinal infection. Progressive weakness, mental depression, severe macrocytic anemia, muscular wasting and emaciation are typical of fully developed cases.<sup>2899</sup> In contrast to pernicious anemia the stomach usually contains free hydrochloric acid. The most important features are diarrhea with pale, greasy foul-smelling unformed watery stools, cramps and distention. Secondary deficiencies develop particularly of the fat soluble vitamins. The characteristic pathologic changes are atrophy of the intestinal mucosa and extreme depletion of the fat reserves of the body. Not too far advanced cases respond to liver therapy in a way similar to pernicious anemia.

The disease is common in some tropical countries, particularly India and perate zones of Europe and America. The infantile form is known as celiac disease.

- <sup>2895</sup>Akhan, K. The Reaction of the Stools and Its Relation to Diseases of the Skin, *Brit J Dermatol.* 51: 18-17 1959.  
<sup>2896</sup>Oellag, J. Dermatitis Follicularis Hyperkeratosis Pruriginosa Ochromatrica—Seccomati Treatment With Charcoal, *Ekt* 38: 483, 1931.  
<sup>2897</sup>Arch. J. J. Association of Intestinal Indigestion With Various Dermatosis—Seccomati & Syph 12: 673-674 1930.  
<sup>2898</sup>Jouliard, H., and Corbier, S. Les modifications cliniques des eczemas au cours de l'évolution de l'eczéma chez le nourisson. *Bull Acad. Med. Paris* III, 104 91-93 1979.  
<sup>2899</sup>Bernard, E. H. and Brabant, J. G. Kruisbuisel und Hartkrakel, *Nederl. Uitskr* 1930 I 1316-1321 *Ekt* 28 240.  
<sup>2899</sup>Porter, O. Ueber den Zusammenhang von Dünndarmerkrankungen und Dermatosen, *Nederl. Uitskr* 1932 I 55-553.  
<sup>2899</sup>Manson-Behr, F. and Willoughby, H. Sprue, 300 Cases, *Quart. J. Med.* 23 11-448 1930.  
<sup>2899</sup>Christians, A. *Oxford Medicine* vol. 2, New York, 1930 Oxford University Press, p. 63.

**Dermadromes**—The long known<sup>300</sup> importance of the mucocutaneous manifestations of the sprue syndrome has recently been re-emphasized by Kaufman and Smith<sup>301</sup>. Glossitis probably reflecting similar changes in the intestinal tract is very common and if combined with characteristic diarrhea is suggestive of the disease.



Fig. 373.—Sprue. Atrophic glossitis and facial pigmentation. (From Manson-Baird Sir Philip Quart. J. Med.)

Stomatitis and glossitis occur in more than 75 per cent of the cases,<sup>302,303</sup> often preceding anemias.<sup>304</sup> The tongue changes involve at first the edges and the tip later the entire surface starting with aphthae or minute shallow ulcers along the edges<sup>305</sup> and inflammation of the fungiform papillae. The sense of taste is often lost in acute sprue and salivation is increased. The glossitis may precede the diarrhea. The tongue is extremely tender especially in the presence

<sup>300</sup>Bahr P. H. A Report on Researches on Sprue in Ceylon, 1912-1914. London, 1912, Cambridge University Press.

<sup>301</sup>Kaufman, W. H. and Smith D. O. Cutaneous Changes in Sprue Syndrome, J.A.M.A. 221 163-172 1942.

<sup>302</sup>Thaynes, T. E. H. Ten Cases of Idiopathic Steatorrhea, Quart. J. Med. 6 239-266, 1934.

<sup>303</sup>Low H. O. Sprue, 180 Cases, Quart. J. Med. 21 323-334 1928.



Fig. 374.—Sprea. Chloasma periorale. (From Kaufman, W. H. and Smith, D. G. *J. A. M. A.*, 1943.)



Fig. 375.—Sprea. Pigmentation of abdomen. (From Manson-Bahr *Brit. Med. Quart. J. Med.*)



of aphthous ulcers. There often are indentations of the edges of the tongue caused by the teeth. Atrophy of the tongue with complete disappearance of the fungiform papillae occurs later<sup>306-308</sup>. In such cases the tongue is narrow and pointed.

The fully developed picture shows absence of the filiform papillae with the fungiform papillae remaining as prominent shiny sometimes hemorrhagic points<sup>304,305</sup>.

Painful rhagades may cut the tongue in both directions. Fissuring of the angles of the mouth is also common. Buccal and infralingual aphthae have been found varying from 22.5 to 67 per cent in large series.<sup>300,302</sup>

The skin is pale dry flabby grayish yellow but not icteric. Large freckles and symmetric chloasma like patchy or diffuse pigmentations have been recorded. Even Addison's disease is sometimes suggested. Some degree of pathologic pigmentation was seen in the majority of the well-observed cases.<sup>304,307,308</sup> Pellagroid pigmented patches on the dorsa of the hands have also been seen<sup>301,307</sup>. The pigment was found iron free thus probably being melanin. The pigmentations in sprue seem to improve with treatment<sup>300</sup> of the disease.

*Intestinal polyposis* may be associated with jet black melanin pigmentation in dots and spots about the mouth the lips and over the hands.<sup>304</sup> Similar pigmentations have been seen in *gastrojejunal colic fistula tuberculosis of the ileum celiac disease*. Jeghers<sup>303</sup> believes that pigmentation without pellagra is more pronounced in diseases of the small intestine than in disorders of the colon. Urbach<sup>10</sup> suggests that the oxidation of phenol substances possibly also of skatol may lead to excessive melanin formation though no proof for this probability has been offered as yet.

**Ulcerative Colitis.**—Nonspecific ulcerative colitis is in about 2 to 3 per cent complicated by skin lesions.<sup>301,302</sup> Most troublesome and conspicuous are ulcerations which may occur<sup>301</sup> on the lower legs. They increase rapidly in size after taking on a kidney shape. They are painful and quite deep but the healing tendency is marked. The appearance and disappearance of the skin lesions may reflect the course but not the extent of the colitis.<sup>30,301,307</sup>

The author observed a case of ulcerative colitis in a woman who after an unhappy married life went through the excitement of a divorce. The periods of worry and excitement not only produced acute attacks of colitis but also new and severe ulcerations of the legs.

<sup>300</sup>Jiargen, J. A. Complications and Sequelae of Chronic Ulcerative Colitis, *Ann. I. t. Med. St.* 33: 342, 1929.

<sup>301</sup>Jiargen, J. A. Present Status of Colitis and Regional Enteritis, *Bull. New York Acad. Med.* 29: 24-25, 1934.

<sup>302</sup>Drumming, L. A. Goekerman, W. H. and O'Leary, P. A. Pyoderma Gangrenosum, *Arch. Dermat. & Syph.* 23: 655-680, 1930.

<sup>303</sup>Jochs, C. M. Peripheral Complications of Ulcerative Colitis, *Med. Clin. North America*, 16: 919-929, 1933.

Pigmentations of the face and body also of the dorsa of the hands may occasionally take on the characteristics of sprue or pellagra. Thickening and distal loosening of the nails may occur<sup>2002</sup>



Fig 376 — Leg ulcers in leucoderma colitis (Courtesy Dr J R Janakides)

Dryness and scaling, follicular keratosis, symmetrical atrophy, pigmentations, various erythemas and cheilitis have been observed and at least in part have been interpreted as a dermatosis<sup>2003 2004 2005 2006</sup>

Tongue and buccal changes occurred in 60 per cent of Mackie's<sup>2007</sup> 75 cases. They may correspond to those in sprue. There was accentuation of the papillae fungiformes, strawberry tongue; the earlier stages and smooth atrophy later. In severe cases, a stomatitis indistinguishable from that in pellagra may develop.

<sup>2002</sup>Milster J J. Proderum, Gangrenosum, Onychocryptosis and Onycholysis With Colitis. Arch. Derm. & Syph. 59: 541-543 1939.

<sup>2003</sup>Mackie T T. Leucoderma Colitis. II. The Factor of Deficiency States, J.A.M.A. 104 172-17 1933.

Whitfield<sup>300</sup> called dermatitis colonica a parapsoriasis like eruption of discrete flat red macules with telangiectases and pigmentation. He connected the dermatosis with colitis and an abundance of streptococci in the stools.

Urticaria seems to be relatively common in colonic disease.<sup>301</sup> The author observed the first outbreak of psoriasis in a man of fifty in typical localization immediately after a colostomy had been performed because of rectal cancer. The patient remained well for two years, but never recovered from his psoriasis. Pruritus without visible skin lesions has been seen in patients with colostomy stomata.

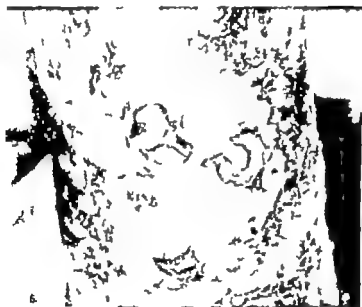


Fig. 377.—*Colitis sicca*. Female aged 32 years. Multiple kidney-shaped rapidly progressing and healing ulcers of the legs. Remarkable parallelism of course of the severe colitis and the ulceration. Both subject to psychogenic influences as demonstrated during the statements of divorce proceedings. Discoloration of the skin is partly due to gun tan violet. (Patient of Dr. Grossberg.)

**Treatment**—If certain dermatoses are caused by pathological contents of the bowel it seems logical to try to treat such skin lesions by the cleansing of the intestinal canal with laxatives, increased intake of water and enemas. These methods are not much used today. However in urticaria and pruritus, catharsis is worth while trying. The use of saline cathartics seems satisfactory. In spite of the good experiences of some authors<sup>302</sup> colonic irrigation has not become a generally accepted method of treatment. Urticaria lichen urticatus, pruritus

<sup>300</sup>Whitfield, A. On Hitherto Undescribed Diseases of the Skin, Brit. J. Dermat. 44: 24, 25, 1922.

<sup>301</sup>Bockus, H. L., Bank, J. and Wilkinson, S. A. Neurogenic Sicca Colitis, Ann. J. M. Sc. 176: 813-839, 1925.

<sup>302</sup>Urbach, E. Das subakute Darmleid. d. Dermatologie Arch. f. Dermat. u. Syph. 190: 233-240, 1920.

and toxicodermas seem to be the dermatological indications for the use of this method. The technique is well described by Urbach<sup>1923</sup> and by Read<sup>1923</sup>. Large doses of activated charcoal to absorb toxic products in the bowel may be used for the same conditions.<sup>1923</sup>

The most important method of treatment consists in the proper diet for which the textbooks of gastroenterology and nutrition may be consulted. Very recently Urbach<sup>24</sup> has presented an excellent modern treatise on the dietary treatment of dermatoses including those of gastrointestinal origin.

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<sup>1923</sup>Read, H. S. Colonie Irrigation, Med. Physics, p. 264, 1944, The Year Book Publishers, Inc., Chicago.

<sup>1924</sup>Chaffaz, J. Dyspeptische Hautkrankheiten, Ebl 35 337

## CHAPTER XLII

# DISEASES OF THE LIVER AND PANCREAS

### The Liver

The bile the secretion of the liver contains bile pigments, bile salts cholesterol lecithin and mucin <sup>229</sup> The pigment bilirubin is a waste product from destroyed erythrocytes which have been collected by the reticulo-endothelial system The liver takes bilirubin from the blood and secretes it into the bile Bilirubin which has passed the liver is slightly different from blood bilirubin This is demonstrable by the two van den Bergh reactions Biliverdin is an oxidation product of bilirubin The bile salts facilitate the action of the pancreas and the absorption of fatty acids Cholesterol is a lipid of the sterol group mainly derived from animal fats The liver supplies most of the blood sugar and forms all the urea It synthesizes most of the fibrinogen thus playing an important role in blood coagulation

Liver damage may result in hemorrhagic disease with prolonged clotting time and prothrombinopenia <sup>230</sup> The liver has a significant detoxifying function Many metabolic and external poisons are either destroyed in the liver or excreted into the bile Disturbance of the detoxifying function of the liver plays an important role in the pathogenesis of allergy The liver is often called the second barrier against poison the first being the intestinal wall <sup>134,242</sup>

**Dermadromes** —*Jaundice* may be caused by *obstruction* in the common duct or in higher parts of the bile duct system provided the dammed up area is large enough The bilirubin is then reabsorbed into the blood There are many causes for such an obstruction the most important being gallstones neoplasms, scarring or inflammatory swelling

In *toxic or infective jaundice* the bilirubin secretion of the liver cells is disturbed Therefore, the blood cannot be sufficiently freed of its bilirubin which soon reaches an icteric level Toxic or infective jaundice is the most common form of jaundice <sup>23</sup> It is encountered in yellow fever Weil's disease typhoid fever pneumonia and other infections in poisonings from chloroform gold arsenobenzol phosphorus carbon tetrachloride some mushrooms e.g. *helvella* and a great variety of other toxic agents

In *hemolytic jaundice* the rate of bilirubin production from destroyed red cells exceeds the capacity of the liver to excrete it The urine as well as the feces retain normal color Some forms of hemolytic icterus are hereditary

These causes of icterus are not always sharply divided. Thus, e.g. obstruction may lead to absorption of bile but also to infection and damage to the liver

<sup>229</sup> Urbach, E. Leber die wechselseitigen Beziehungen zwischen Leber und Haut, Arch. f. Dermat. u. Syph. 178 767 787 1937

cells with subsequent failure to drain bilirubin from the blood. Jaundice is probably the most regularly encountered skin manifestation of any internal disorder.

The color of jaundiced skin varies widely from a slightly yellow tinge to lemon greenish brown or even purplish shades. Greenish jaundice is explained by cyanosis; brown or black hues come about by combination with various pigmentations. Orange or saffron color of the skin suggests intrahepatic jaundice; greenish to bronze obstructive jaundice. A greenish tint may develop in intrahepatic jaundice in the presence of liver necrosis and also in the receding stage of jaundice.<sup>306</sup> Yellowish blue or green is considered almost diagnostic of a tricuspid lesion or a relative insufficiency of the valve (Wearn after Jeghers<sup>307</sup>).

The distribution of jaundice is not always even. In slight and early cases only the sclerotics or the hard palate may appear yellow. In catarrhal icterus the discoloration usually appears on the head, neck, the upper trunk, the abdomen, the legs and finally on the forearms and hands.<sup>307</sup> The jaundice may come on in repeated attacks, each increasing the color of already yellow areas. At the height of the icterus the areas which appeared first are then the darkest. Thus the upper part of the body is generally darker than the lower part.<sup>308-309</sup> The regression of icterus follows the reverse order of its appearance, so that sclerotics and face may still be yellow when all other parts have reached a normal color. The differences in intensity are not yet sufficiently explained. Differences in concentration and in the amount of blood which during a given time, flows through and stains the areas are likely to cause difference of intensity of color.

Hyperemia or urticaria causes local increase of the icterus probably because of greater capillary permeability; this is easy to demonstrate under glass pressure. In subclinical icterus the hyperemic halo of a histamin reaction leaves a yellow ring after the hyperemia has disappeared. With this skin test a bilirubin level of as low as 1 mg. per cent can be shown.<sup>310</sup> The remaining local icterus after disappearance of urticaria factitia is called yellow dermatographia.<sup>311</sup> It may be present prior to clinical icterus. Two cases of contralateral jaundice and ipsilateral edema in apoplexy and cardiac decompensation have been described by Page.<sup>312</sup> It has been suggested that in these instances the edema prevented the entrance of the pigment but this is unlikely since a local edema like a wheal increases icterus.

Localized jaundice about the umbilicus due to rupture of the common bile duct was described by Rauehoff (see Jeghers)<sup>313</sup>

<sup>306</sup>Lichtman: *Disease of the Liver*, Philadelphia, 1942, Lea & Febiger.

<sup>307</sup>Kovacs, I.: *Leber die Vererbung des H. Icterus*, Wien klin. Wchnschr. 1923 II 1446-1457.

<sup>308</sup>Umbor, F. and Rosenberg, M.: *Regionärer Icterus*, Deutsche med. Wchnschr. 51 90-91, 1925.

<sup>309</sup>Schick, D.: *Die Vererbung der Gelfärbung in der Haut beim Icterus neonatorum*, Ztschr. f. Kinderh. 23: 13-230, 1924.

<sup>310</sup>Jerabek, E.: *Neues Regel der früh beobachteten Abheilung im Verhältnis zum Hämoglobin*, Wien klin. Wchnschr. 1929 I 573-57.

<sup>311</sup>Klein, O.: *Nachweis von icterus durch intradermale Rhodaninjection*, Klin. Wchnschr. 1931 II 2022-2025.

<sup>312</sup>Davis, A. J. and Engelhardt, H. T.: *Yellow Dermographia*, Arch. Dermat. & Syph. 68 310-311, 1942.

<sup>313</sup>Rauehoff: *Localized jaundice about the umbilicus*, Arch. Intern. Med. 1911 16: 100-101.

Several tests using injection of dyes into the skin have been devised to demonstrate subclinical icterus<sup>3023</sup> but none has become important since accurate quantitative determinations of bilirubin in the serum are now generally made with the van den Bergh method. Intracutaneous injection of 1 per cent potassium ferricyanide produces a blue spot if the icterus is caused by an iron containing blood derivative. This is known as the positive Brugach test<sup>3024</sup>. Bilirubin is iron free. The value of the Brugach test for iron has recently been doubted<sup>3025</sup>. The extrahepatic type of icterus is seen in the presence of very numerous skin hemorrhages which may cause generalized yellow discoloration. The Brugach test is also positive in icterus neonatorum.

Itching sometimes restricted to some areas is a common and troublesome though not invariable symptom of icterus. It is absent in hemolytic icterus<sup>3026</sup>. It is controversial whether the presence of bile salts and bilirubin is responsible for the pruritus. Insulin in doses of 20-50 units daily seems to relieve the itching<sup>3027</sup>. In senile and other types of pruritus sine materia tests sometimes indicate an impaired liver function<sup>3027</sup>.

The capillaries of icteric skin are more permeable than those in the normal skin.

Urticaria is frequently seen. The icteric skin develops a wheal after injection or iontophoresis of a one hundred times weaker histamin solution than is necessary to create the same effect in the normal skin<sup>3028</sup>. Cantharides draw blisters in a shorter time in icteric than in normal skin<sup>3029</sup>.

The disappearing time of an intracutaneous wheal of isotonic salt solution (McClure and Aldrich Test<sup>3030</sup>) is shortened in icterus.<sup>3031</sup>

Long lasting jaundice with hypercholesterolemia, as in biliary cirrhosis may produce xanthomas in the skin. One has to look for these lesions in the creases of the finger joints and about the elbows. These xanthomas are reversible with changes in the blood cholesterol<sup>3032</sup>.

✓*Liver spots* are chloasma like hyperpigmentations in the face, caused by melanin deposits. They are suggestive of liver disease but are neither frequent nor specific. The French term *masque biliaire* is applied to a periorcular chloasma hepaticum.

The hemorrhagic tendency<sup>3033</sup> may be severe however it is not parallel to the icteric indexes<sup>3034</sup>. It constitutes an added risk in any surgery on a jaundiced patient. Gastrointestinal bleeding is usually the first hemorrhagic symptom in obstructive jaundice. An alarming picture of hemorrhagic disease

<sup>3023</sup>Dodd O. Sulla ricerca della bilirubina nella pelle degli itterici, Riv di Clin med 22 501 1906 831

<sup>3024</sup>Brugach T Zur Analyse des Icterus, Deutsche med Wchnschr 1929 I 547-548

<sup>3025</sup>Roersdal F Hautjucken bei Ikterus Therap d Gegen 78 297-301 1929

<sup>3026</sup>Malamed T Insulin beim Pruritus der Ikteruskranken, Prensa med argent. 17 1234-1236, 1931 231 23 494

<sup>3027</sup>Hibber K Hyperbilirubinemia Pruritus, Arch of Dermat Syph. 178 509-514 1937

<sup>3028</sup>De Tullio R La permeabilità dei capillari linf. infiammatorio della cute negli epato-patisti, Riforma med 46 341-344 1928

<sup>3029</sup>Mora, J M and Jirka F J The Effect of Jaundice on Intradermally Injected Salt Solution, J Lab & Clin Med 30: 719-723 1935

<sup>3030</sup>Confort M W Shepard V O and Sewell A M Xanthomatous Biliary Cirrhosis, Proc Soc Med., Mayo Clin 38 374-377 1941

may follow.<sup>290</sup> Quick emphasizes the absence of petechiae and the presence of large ecchymotic areas.

The lack of vitamin K, which maintains the normal level of serum prothrombin, is now recognized as the cause of the hemorrhagic disease in obstructive jaundice with not too much damage to the liver.<sup>290,291</sup>

Extensive liver damage, whether primary or secondary, may account for the inability of the liver to produce prothrombin. The resulting hemorrhagic tendency is due to hypoprothrombinemia and is not relieved by vitamin K.<sup>290,279</sup>

**Cirrhosis of the Liver**—In portal cirrhosis the skin is usually grayish or sallow. Icterus often little pronounced, is seen in 30 to 88 per cent of the cases.<sup>292,293</sup> Pruritus is common. Urbach<sup>292</sup> has produced considerable evidence



FIG. 274.—Cirrhosis of the liver. Large arachnoid spider angioma in clavicle surrounded by several small spiders. (From Braun, W. H., *Medicine*.)

tracing the pruritus in hepatic cirrhosis to the disturbed protein metabolism of the liver. While there are no conspicuous dermatromes, the frequent appearance of spider-like telangiectases is of theoretical and to some extent prognostic interest.

<sup>290</sup>Urbach, R. R. The Diagnosis and Treatment of the Purpuric Diseases. South. M. J. 24: 24-8, '31.

<sup>291</sup>Parke, J. D. and Thompson, F. L. 71 Cases of Cirrhosis of the Liver. Ann. Ent. Med. 21: 253-277, 1941.

<sup>292</sup>Urbach, R. R. and Parke, J. D. The Natural History of Langer's Cirrhosis of the Liver. Ann. Ent. Med. 21: 207-208, 1942.



## PLATE VI

- 1 Herpes simplex, seen in many forms.
- 2 Hepatic cirrhosis. Ascites, congested veins, biliary lipocelia, pigmented male nipple. Not absence of striae.
- 3 Hepatic cirrhosis. Erythema of the palmar eminences, so-called liver palms and vascular spider in unusual location.
- 4 Hepatic cirrhosis. Vascular spider.
- 5 Biliary cirrhosis. Four years after ligation of common duct, jaundice.
- 6 Biliary cirrhosis. Bleeding gums, decayed teeth.



PLATE VI



*Vascular spiders* (cutaneous arterial spiders,<sup>304</sup> *nevus araneus* like or stellate lesions, *tache stellaire étoile vasculaire*) were first described in an alcoholic (hepatic cirrhosis) by Erasmus Wilson.<sup>305</sup> Their physiology, histology and clinical significance has recently been studied by Patek, Jr Post and Victor<sup>306</sup> Bean<sup>304</sup> and many other authors particularly French.

The vascular spider consists of a 'body' which is a central raised pin head to lentil-sized papule from which the 'legs' spokes or radicles radiate. The latter are telangiectases which branch out and anastomose in many ways. An area of erythema often surrounds the central punctum and an anemic halo around the red area is occasionally visible. The color of the central eminence is bright red but does not show well in infra red photography<sup>304</sup> which is one of the proofs of its arterial nature. Veins appear darker in infra red. The temperature of the vascular spider is 2.3° C (3.5° F) higher than the normal skin surface. The blood flows from the center to the periphery and pulsation can usually be demonstrated if controlled glass pressure is applied. The intravascular pressure, as measured by the force necessary to stop the pulsation and blanch the lesion is between 70 and 90 mm of Hg. Adrenalin blanches the finer ramifications and histamine deepens the red area more than the adjacent skin. The number of spiders varies from a single one to an occasional exanthem of the density of mild chicken-pox. This, however is rare. The spiders are, with few exceptions restricted to the upper half of the body with a predilection for the neck clavicular areas and face. The pattern of distribution reminds of sites of benign new growths under estrogenic influence (see pregnancy and menopause). The palms are more often affected than the arms. Scattered or reticular fine telangiectases may be seen together with the spiders indicating the widespread alteration of the capillaries. Bean<sup>304</sup> aptly compares this type of telangiectases with paper money flecked with silk threads.

Besides the *nevus araneus*-like lesions simple telangiectases in small plaques at the costal arch were described by Galloway<sup>307</sup> in various visceral conditions with stasis including cirrhosis.

Stellate telangiectases in cases of Laennec's cirrhosis, have been found in 15 per cent by Ratnoff and Patek,<sup>308</sup> 56 per cent by Cirovacki (after Bean) and 75 per cent by Bean<sup>304</sup> but they are also encountered in other liver diseases e.g. in catarrhal jaundice in Weil's disease and in common duct stone with jaundice though decidedly less often.<sup>304</sup> The chronicity of the disease does not seem to have much bearing on their development since they have rarely been found in hepatic carcinomatosis. It can generally be said that the presence of spiders indicates a more severe cirrhosis.<sup>304</sup> Improvement of the hepatic condition may be followed by disappearance of the spiders.

The histological<sup>304 306 309</sup> character of the spider is that of a coiled artery larger than that ordinarily found in the surface of the skin. The arterial wall has

<sup>304</sup>Bean W. I. The Cutaneous Arterial Spider. A Survey. *Metastases* 24: 212-221, 1912.

<sup>305</sup>Wilson, E. Eruptive Anomalies. *J. Cut. Med. & Dis.* 18: 189, 1899.

<sup>306</sup>Patek, A. J. Jr Post J. and Victor J. The Vascular Spider. Anemia of the Liver. *Am. J. Med.* 2001: 1-3, 1950.

<sup>307</sup>Galloway J. Vascular Lesions of Visceral Diseases. *Brit. M. J.* 1905: 1: 885-887.

<sup>308</sup>Ratnoff A. Cirrhosis of the Liver With Stella Telangiectases of the Skin. *Schweiz. Ztschr.*

*f. Path. Bakt.* 57: 2-7, 1952.

some characteristic of the arterial segment of an arteriovenous anastomosis (glomus). The spider is decidedly different from a hemangioma.

The free urinary *estrogen* values in advanced cirrhosis are high and the androgen values are low<sup>140</sup>. The diseased liver seems unable to inactivate



FIG. 379.—Hepatic cirrhosis, gynecomastia.



FIG. 380.—Hepatic cirrhosis, pigmented and enlarged male nipple.

estrogens<sup>3043</sup> and the testicular atrophy which is common in fully developed cases, probably accounts in part for the lack of androgens. Androgens continue to be inactivated by a liver which has been damaged enough to be unable to inactivate estrogens. Thus the balance between estrogens and androgens is upset.<sup>3043</sup> These endocrine disturbances help to explain the production of spiders, palmar erythema and chloasma which also occur in pregnancy and which can be provoked by administration of estrogens to cirrhotic patients<sup>3044,3045</sup> The low level of androgens may increase the effect of the high estrogens. This may also account for the gyn-



Fig 241.—Hepatic cirrhosis. Axillary hyperaemia, enlarged male nipple

comastia which is frequently present in advanced cases. Paula<sup>3046</sup> found gynecomastia with increase of milk ducts, cyst formation and milk secretion in 5 out of 7 autopsies.<sup>3046</sup> The nipples are often enlarged, cylindric and erect, the areola deeply pigmented. The loss of axillary and to a lesser extent pubic hair<sup>3047</sup> is common in cirrhosis. This symptom may also be related to endocrine disturbances especially testicular.

<sup>3043</sup>Dickel, M., Weiland, R. and Weiland, L. H.: Vitamin Deficiency in the Etiology of Metrorrhagia, Metrorrhagia, etc. Mistle and Premenstrual Tension. II. Treatment With Vitamin D Complex. *May Gynec & Obst* 78: 49-57, 1941.

<sup>3044</sup>Heas, W. B.: A Note on the Development of Cutaneous Arterial Spiders and Palmar Erythema in Persons With Liver Disease and Their Development Following the Administration of Estrogens. *Am J Med Sci* 223: 251-253, 1941.

<sup>3045</sup>Heas, W. B.: Acquired Palmar Erythema and Cutaneous Vascular "Spiders." *Am Heart J* 25: 472-477, 1943.

<sup>3046</sup>Paula, F.: Gynecomastie und Leberzirrhose. *Deutschsch Arch f klin Med* 100: 62-69, 1930.

<sup>3047</sup>Marion, E.: Syndrome pœux. *Malad Rev Méd de la Suisse Rom* 51: 574, 1931. *EM* 29: 745.

*Erythema of the palmar eminences* (liver palms) especially of the hypothenar often associated with spiders was observed in about 25 per cent of the patients with cirrhosis<sup>204</sup> but only in 4 per cent of Ratoff and Patek's<sup>205</sup> 386 cases. The condition also occurs in other internal disorders e.g. gastrointestinal ulcer rheumatoid arthritis heart disease chronic sepsis, pulmonary tuberculosis chronic deficiency states and in pregnancy. It is also occasionally seen in normal persons. Palmar erythema, like its related lesion the vascular spider may wax and wane with fluctuations in the severity of the liver disease.<sup>204</sup> It has been

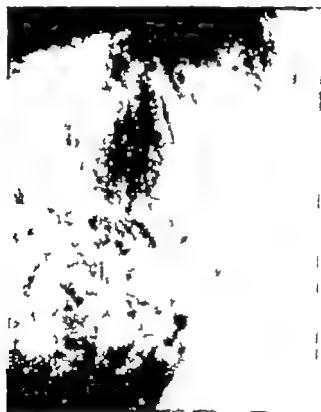


Fig. 283 — Hepatic cirrhosis axillary alopecia. — Male aged 50 years.

shown that palmar erythema can be provoked by potent estrogens in persons having some of the mentioned diseases.<sup>206</sup> The erythema is arterial in character and warm to the touch. The capillaries are increased. The palmar erythema is sometimes combined with erythema of the fingertips, clubbing of the end phalanges and Hippocratic nails.

The well known appearance of *dilated veins* around the navel (*caput medusae*) is relatively rare. Congested veins are of frequent occurrence in the presence

<sup>204</sup>Parry, G. A. A Note on Palmar Erythema (So-Called Liver Palms). *J. A.M.A.* 119: 1417 1943.

of ascites.<sup>360</sup> In more than 40 per cent of the cases<sup>360</sup> dilated veins in the skin of the abdominal and thoracic walls show the existence of an established collateral circulation. Infrared photography may detect tortuous veins before they become visible. Edema of the ankles occurs in the majority of the cases. Hemorrhoids are seen more frequently in cirrhosis than in comparable groups (Chapman Snell and Rowntree after Ratnof and Patek<sup>360</sup>). Hemorrhagic phenomena are observed in about 33 per cent of the



Fig. 242 - Biliary cirrhosis. Stuck tongue



Fig. 243 - Xanthoma on between palpebrae in patient with biliary cirrhosis



cases of cirrhosis. One-third of the hemorrhagic patients show purpura.<sup>2003</sup> Striae are absent.

In *biliary cirrhosis* the jaundice is severe. Bleeding from the gums is frequently seen. Xanthomas in the palmar creases, the soles and elsewhere may develop in hyperlipemia.<sup>2004</sup>



Fig. 285.—Cachexia (biliary cirrhosis).—Hippocratic nails.

**Gallstones and Cholecystitis.**—Little is known of skin manifestations in diseases of the gallbladder. The infected gallbladder may become a focus of infection and cause cutaneous lesions.<sup>2005</sup> A stone in the common duct may cause icterus with its cutaneous sequelae. Xanthoma especially of the lower eyelid, salivation, gingivitis, transient yellow or persistent chloasmatic spots on forehead and cheeks, urticaria,<sup>2007</sup> pruritus and telangiectases are occasional manifestations of chronic cholecystitis.<sup>2008</sup>

**The Liver in Dermatoses.**—Many investigators<sup>2009</sup> have studied liver functions in skin diseases. This has been done with most of the liver function tests (for a practical appraisal of the liver tests see Ivy and Roth<sup>2000</sup>) especially the two van den Bergh tests, the determination of urobilin and urobilinogen in the urine, blood sugar tolerance tests, galactose, gelatine and water<sup>2001</sup>, phenol, tetrachl. rphthalein sodium<sup>2002</sup>, Vidal's hemophilia<sup>2003</sup>, Falet's bile tolerance test

<sup>2000</sup>Kutsumura O. B. and Montgomery H. Disorders of Liver and Extrahepatic Biliary Ducts Associated With Cutaneous Xanthomas and Hyperlipemia, *Gastroenterology* 3: 273-280, 1944.

<sup>2001</sup>Lane C. W. and Hirsch C. M. Pruritus. *Gastroenterology*, *Arch. Dermat. & Syph.* 27: 480-486, 1935.

<sup>2002</sup>Meacham F. R. Etiology and Results of Treatment in Anaphroretic Edema and Urticaria, *J. A. M. A.* 90: 654-671, 1926.

<sup>2003</sup>Delaunay J. De quelques signes hépatiques et cutanés dans les cholestases et les autres dysdomies. *Bull. soc'd* 1931, 11: 823-826. *Sibl.* 61: 78.

<sup>2004</sup>Doboway M. Korrelation zwischen Haut und Leber. *Dermatologica* 70: 370-391, 1932.

<sup>2005</sup>Ivy A. and Roth J. A. What is Liver Function Test? *Gastroenterology* 1: 633-663, 1942.

<sup>2006</sup>Doffles H. Leberfunktionsprüfungen I. *der Dermatologica*, *Arch. f. Dermat. u. Syph.* 190: 405-406, 1933, 190: 486-487, 1934.

<sup>2007</sup>Matsunobu T. Xanthoma and Liver Function, *Eczema and Sugar Metabolism*, *Jap. J. Dermat.* 30: 825-828, 1920. *SKN* 27: 255.

<sup>2008</sup>Yachi K. Liver Function in Skin Diseases, *Jap. J. Dermat.* 38: 611-672, 1924. *SKN* 43: 491.

and the determination of urobilinogen in the stools after Schmidt<sup>303</sup>. Other investigations were concerned with the reticulo-endothelial system of which the Kupffer cells in the liver represent an important part. The disappearance of intravenously injected congo red from the blood (Adler and Reimann test) was used as an indication of the function of the reticulo-endothelial system in the liver<sup>304</sup>. The reticulo-endothelial system of the skin was studied in this connection by von Leaczynski and his collaborators<sup>305</sup> mostly with intracutaneous injections of histamin morphin caffeine pilocarpin and trypan blue. The results of the many investigations of liver function in dermatoses are not consistent. Hepatic dysfunctions were found in eczema<sup>306,307,308</sup> acute exudative dermatoses,<sup>309</sup> urticaria dermatitis after arsenphenamines<sup>310,301,300</sup> and other drug eruptions.<sup>307</sup> In the larger series the patients with disturbances ranged from 10 to 40 per cent. The high incidence of liver disorders in photodermatoses, drug eruptions, rosaces and other dermatoses characterised by widespread new formation of capillaries is emphasized by Milbradt<sup>300</sup> and many others.

*Porphyria* and increased fecal porphyrin which often accompany photodermatoses e.g. hydros vacciniforme, is probably the expression of a disturbed liver function<sup>19,300-302</sup>. The combination of alcoholism and syphilis is apt to create the conditions which lead to hepatic cutaneous porphyria and photodermatoses. In porphyria and hydros the mechanical vulnerability of the skin may be much increased so that slight trauma may cause blisters and oozing defects.<sup>307,3073</sup> Thus an epidermolysis bullosa-like picture may ensue.<sup>307,3073</sup> Photodermatoses with an hepatic background and hyperporphyrinemia or porphyria may also appear as xeroderma pigmentosum<sup>3077</sup> eczema urticaria, erythema multiforme and prurigo.

*Xanthomas* including the common xanthelasmata of the eyelids, should always arouse the suspicion of liver disease. Icterus is frequently found in xanthoma and even in its absence liver disorders may well be detected by function tests (Hübner after Urbach<sup>3073</sup>).

- <sup>304</sup>Fackl, O. Rikrechl mit funktioneller optisch-nerf. oedem, Olor bei di. dermat. u. all. 80  
704, 1927
- <sup>305</sup>Kordowich, F. d. Methylenblaubestimmung bei Hautkrankheiten. Arch. f. Dermat. u. Syph.  
178 117-122, 1937
- <sup>306</sup>Marquard. Porphyrie im Urin bei Hauterkrankungen. Zbl. 82 523-526, 1936.
- <sup>307</sup>Milbradt, W. Haut und Organerkrankungen. Leberstoffwechsel. Med. Welt 9 1417-1421 1933.
- <sup>308</sup>Carrié, C. Hydros vacciniforme und Porphyriae. Arch. f. Dermat. Syph. 163 523-525  
1931
- <sup>309</sup>Strasser and Urbach. Hydros vacciniforme mit Porphyriae. Wien. med. W. hscrh.  
231 II 1206-1207
- <sup>310</sup>Bruckner, L. A. Bruckner, J. T. and O. Leary P. A. Porphyria Met. bolism in Diseases of the  
Skin Arch. Dermat. & Syph. 59: 291-307 1951
- <sup>311</sup>Urbach, E. Hydros vacciniforme. Leber und Milchzucker. Porphyriae. Zbl. 82: 149  
1936
- <sup>312</sup>Urbach, E. and Rösch, J. Hydros Vacciniforme. Porphyriae. Die Hepatops. bei Wien.  
k. k. Wchnscr. 47 527-532, 30
- <sup>313</sup>Gottron, H. ad Eitner, F. Porphyrie. Arch. f. Dermat. u. Syph. 164 1-42 1921
- <sup>314</sup>Gottron, H. Epidermolysis bullosa-artiges Krankheitsbild bei Porphyria. Dermat. Wchnscr.  
161 1201, 1925
- <sup>315</sup>Tarant, W. J. ad Obermeyer, M. E. Porphyria With Epidermolysis Bullosa, Hypertrichosis  
and Milium Arch. Dermat. & Syph. 87: 9-272, 1939
- <sup>316</sup>Hübner. Die Xeroderma pigmentosum var. phthiomas et types divers. Hoff. für Derm.  
Dermat. 2: 74-76 1931. Zbl. 89: 542
- <sup>317</sup>Urbach, E. Pigment. Lich. dermat. oem. auf Grundlage von toxischer pathologischer Porphyria.  
bildet im Darm. Infekt. Dysbal. erie und Hepatops. bei Klin. Wchnscr. 57 201-210 (1937)

Clinical experience has often shown that psoriasis, eczema urticaria <sup>246,2467,2472</sup> Quincke's edema rosacea and other dermatoses followed the ups and downs of liver or gallbladder disease and cleared up after their successful treatment. An impressive group of such cases was presented by Smilthies,<sup>2098</sup> who used drainage of the duodenum mostly combined with a diet low in fat and protein and stimulation of the flow of bile by magnesium sulfate.

The opinions about associated liver disturbances in psoriasis are divergent.<sup>2467,2462</sup> The possibility of liver damage secondary to skin disease must be recognized. This is based on observations in burns and in the experimental croton oil dermatitis of rabbits.<sup>2462</sup> Dubow<sup>2463</sup> found hepatic dysfunction regularly connected with a disturbed RES of the skin.

Liver extract has been found a useful adjunct in the treatment of many skin diseases.<sup>2462</sup> Exfoliative dermatitis due to arsenphenamine is an example.

### The Pancreas

The pancreatic juice neutralizes the gastric acidity, splits proteins down to amino acids (trypsin), fats into glycerine and fatty acids (lipase) and converts starches into sugar (amylase). The best known hormone of the pancreas is insulin which helps to burn sugar stimulates the formation of glycogen in the liver and muscles and probably inhibits glucose formation from amino-acids in the liver.<sup>1298</sup> In pancreatectomized dogs the liver becomes fatty. This can be prevented by an alcoholic extract of pancreas. Dragstedt's lipocatic.<sup>1299</sup>

Kallikrein (padutin) is a pancreatic hormone with a vasodilating effect. It can to some degree neutralize the effect of adrenalin. The most important skin manifestations of pancreatic disorders are those occurring in diabetes (see chapter on diabetes). Our knowledge of other pancreatic dermadromes is scanty.

**Dermadromes of Pancreatic Diseases.**—Chronic pancreatitis and other benign disorders may provoke urticaria,<sup>2467</sup> eczema, pruritus ani<sup>2462</sup> and other nonspecific dermatoses. The disturbance of fat digestion has been related to some cases of eczema,<sup>2462</sup> especially in infants.<sup>2464</sup> The administration of pancreatic substance by mouth has been recommended.

**Acute necrosis of the pancreas** (acute pancreatitis) is occasionally accompanied by deeply cyanotic livedo-like or spotty venous patterns (Wahsted after Moynihan<sup>2465</sup>) covering the abdomen, chest and thighs.<sup>2466</sup> A palm-sized dirty

<sup>2098</sup>Smilthies H. Urticaria and Cholelithiasis, Wien klin. Wchnschr. 66: 81-82 1927

<sup>2462</sup>Smilthies F. Defective Liver Functions as Cause of Chronic Exfoliative Skin Lesions, Ann. I. L. Med. 3: 130 240 430

<sup>2467</sup>Marcel J. Chronic Relapsing Urticaria and Angioneurotic Edema, Arch. Dermat. & Syph. 29: 993-994, 1929

<sup>2468</sup>Quinby W. A. Roentgen Ray Diagnosis of Chronic Pancreatitis and Its Relation to Common Skin Diseases, J. Radiol. 5: 186-196 1926

<sup>1298</sup>Ayres, S. J. in due to Stokes and Pillsbury Arch. Dermat. & Syph. 22: 800, 1930

<sup>2464</sup>Korda, F. Eczemas as Nebenleiden d. Nourishment, Sebana mfd. 29: 81-86 1922 Ed. 12: 265

<sup>2465</sup>Moynihan B. Act. Pancreatitide Ann. Surg. 61: 123-42, 1925

<sup>2466</sup>Wahner P. Symptom der Becken-und gitterförmigen Cyanose bei acuter Pankreasnekrose, Wien. klin. Wchnschr. 66: 218-219 1927

gray-green slightly raised discoloration has been observed around the navel or in the lumbar area, probably caused by direct leakage and autodigestion. This is known as *Turner's sign*<sup>3035,3037,3042</sup>. The abdominal cyanosis is not seen in the majority of the cases.<sup>3042</sup> It is considered a pathognomonic sign.

*Cancer of the head of the pancreas* causes intense obstructive sometimes blackish jaundice (ictère noir)<sup>1879</sup>. In 56 per cent of the autopsied cases of cancer of the body or tail of the pancreas, at least one thrombosis was found.<sup>3040</sup> In about one-third of the cases the venous thromboses were widely disseminated. Usually there was no jaundice present. Thromboses of veins in both lower legs with acute cutaneous inflammation may be the presenting symptom of carcinoma of the pancreatic body.<sup>3041</sup> No mention of thromboses is made in a recent review of 52 cases of pancreatic carcinoma.<sup>3043</sup> The thromboses may affect any of the great veins of the body. The neoplasms were all of the mucinous type.

Pancreatic extracts, especially lipocalc and depropanex have given encouraging though not striking results in psoriasis.<sup>3044,3045</sup>

The insulin free pancreatic extract padutin or kallikrein<sup>3046</sup> and similar preparations<sup>3047</sup> has been used in Raynaud's disease acrocyanosis and related peripheral vascular disorders. It has also given some results in scleroderma<sup>3048</sup> of the morphea type.

<sup>3035</sup>Kaafjer J H. Hautverfärbung bei akuter Pankreasnekrose, *Wch. f. Chir.* 63: 240-251 1935.

<sup>3037</sup>Turner G. Local Discoloration of the Abdominal Wall as Sign of Acute Pancreatitis, *Brit. J. Surg.* 7: 304-305 1919-1920.

<sup>3038</sup>Leckson, E. B. Acute Pancreatitis. 39 Cases, *Ann. Surg.* 116: 367-373, 1942.

<sup>3039</sup>Spiegel, E. E. Carcinoma and Venous Thrombosis, *Am. J. Cancer* 31: 544-553, 1935.

<sup>3040</sup>Kaasey W. E. Carcinoma in Head and Tail of Pancreas With Multiple Venous Thrombi, *Surgery* 14: 800-809 1943.

<sup>3041</sup>Schneider, J. G. and Orr T. G. 28 Cases of Carcinoma of Pancreas and the Absence of V. for *Ann. Surg.* 114: 802-811, 1941.

<sup>3042</sup>Walsh, E. H. Clark, D. B. Dragstedt L. R. and Baker G. W. Lipocalc in the Treatment of Psoriasis, *J. Invest. Dermat.* 4: 86-87 1941.

<sup>3043</sup>Dawkins J. G. Glicksberg, H. A. and Miesner, S. J. Deproteinized Pancreatic Extract in Treatment of Psoriasis, *Arch. Dermat. & Syph.* 48: 1138-1137 1942.

<sup>3044</sup>Frey H. K. Ein neues körperl. Sekret des Pankreas, das Kretinohormon Kallikrein, od seine therapeutische Verwendung, *Deutsche Zeitsch. f. Chir.* 233: 481-516 1931.

<sup>3045</sup>Adel, J. Zur Behandlung der Acroterangiitis atrophicans mittels der Pankreasextrakttherapie *Dermat. Wochenschr.* 1933: 540-548.

## CHAPTER XLIII

### DISORDERS OF THE RESPIRATORY TRACT\*

Generally the incidence of dermatoses in very large numbers of institutionalized pulmonary patients was below the average of the general population.<sup>100</sup> This seems to be due to the sheltered life and the absence of occupational hazards.

Cyanosis is marked in many respiratory diseases. The blue discoloration may be of short duration as for example in the whooping cough attack or it may be longer as in diphtheria some cases of pneumonia pleuritis emphysema or large mediastinal tumors.

The frequency of acrocyanosis and erythrocyanosis in a series of about 5000 cases of pulmonary tuberculosis is emphasized by Szanto.<sup>101,102</sup> Papulonecrotic and indurative tuberculous lesions have been described in connection with acrocyanosis<sup>103,104</sup> and livedo racemosa. Women are particularly subject to acrocyanotic conditions which may account for the female dominance in tuberculosis indurativa (erythema induratum).

Telangiectases on the thorax are said to occur in 45 per cent of patients with pulmonary tuberculosis. They are called *Fränke's striae* a misnomer since they are actually telangiectases and not atrophies.<sup>105, 106, 107</sup>

These telangiectases are at most 1 cm. long straight curved or branched thin sharply drawn blood vessels in the skin over the upper dorsal vertebrae and along the costal arch in front of the anterior axillary line. The latter are much more common; men (11 per cent) the former about equally frequent (3 per cent) in both sexes.<sup>108</sup> *Fränke's striae* seem to be independent of the severity of the lung process but more apt to occur in cases of long duration. They are probably due to lung and pleural involvement adjacent to or underlying the respective skin areas. The telangiectases are not characteristic of tuberculosis since they are encountered in normal persons and also in emphysema. They are common in elderly men.

Sorgo<sup>109</sup> found the skin over parietal pleuritic lesions thicker and slightly edematous. It is consistent with this observation that hypodermic injections of 1 per cent solution of congr. red into symmetric sites of the thorax showed in 36 out of one hundred patients with pulmonary tuberculosis a larger spot on the diseased side.<sup>110</sup>

\*This chapter includes the nonspecific dermatoses of pulmonary tuberculosis.

<sup>100</sup>Szanto J. Has verändert sich bei Lungentuberculose, Dermat. Wochschr. 1929 II 1899-1908.

<sup>101</sup>Hansen Miva J. Acrocyanosis and Papulonecrotic Tuberculosis. Ber. hessl. Ges. Derm. 8 809-1006 1934. Zbl. H. 1.

<sup>102</sup>Comessatti R. and R. de. Complesso quadro di tubercolosi in acrocianotici. Una tal. di dermat. di 73 (9 1931).

<sup>103</sup>Almquist L. T. Angio- und erythrocytose bei acrocyanotischer Tuberculose, Ritz. dermat. Klin. d. Tuberk. 4 509-514, 1930.

<sup>104</sup>Ossola M. V. Fünf neuartige Erscheinung des Morgenschen Hauttuberkulosephänomens. Wien. klin. Wochschr. 1935 I 367.

*Striae thoracicae* in lung disease have been discussed under the heading *striae*.

A rapid course in pulmonary tuberculosis often increases the *succulence* of the skin. In chronic cases the skin is more apt to be thin and dry—even diffusely atrophic resembling senile skin. Szantó<sup>73</sup> considers these changes as nonspecific and inherent to the severe disease.

*Fungus diseases* are frequent. *Pityriasis versicolor* once considered a characteristic accompaniment of pulmonary tuberculosis, has become relatively rare 1.5 per cent.<sup>74</sup> This is probably due to better bathing conditions. However it is still three times more frequent among the dermatoses of the inmates of lung sanitariums than among the dermatoses of nontuberculous groups. The incidence of epidermophytosis is 6 times greater<sup>75</sup> sweating probably being a factor.

Many statistics emphasize the high incidence of *acne* among the patients of lung sanitariums. The percentages range from 7 per cent<sup>76</sup> over 12 per cent<sup>77</sup> to about 40 per cent.<sup>77,78</sup> However these statistics lack comparable controls in the corresponding age classes of the healthy population. Overeating of fats during dietetic treatment may be responsible. The more severe *acne dorsalis* is often found over the site of the greatest pulmonary involvement.<sup>77,78</sup> Szantó<sup>74</sup> in his very large series confirms the relatively great frequency, severity and incidence in age groups up to 40 and 50 years. Exacerbation of *acne* after artificial pneumothorax has been observed by several authors.<sup>77,78</sup> Shoji<sup>79</sup> found the eyelashes of patients with pulmonary tuberculosis to be longer than those of normal controls. *Chloasma* was found twelve times more frequently than in the general population.

Since it had been suspected that pulmonary tuberculosis in *red-haired* persons takes a more rapidly fatal course, Bogen<sup>80</sup> compared a group of red haired persons with the average of 10 000 other patients with pulmonary tuberculosis. No significant differences in the fatality rate could be found.

The pressure in the *skin capillaries* was found higher in fibrotic pulmonary tuberculosis than in exudative forms.<sup>81</sup> In a series of 241 cases of pulmonary tuberculosis, the capillaries of the nailbeds of the fingers on the side of the more active lung lesion were found more dilated than on the other side. The side of gross fibrosis and caverns is often marked by deformed capillaries on an anemic background.<sup>81</sup>

*Bronchial asthma* is sometimes combined with eczema of the flexor surfaces. Alternating between eczema and asthma also familial accumulations of both

<sup>73</sup>Szantó, I. Hauterkrankungen bei Kranken mit Lungentuberkulose, *Dtsch. Tbk. H.* 50-56 1933 Ed. 47-57.

<sup>74</sup>Friedl, K. Lungentuberkulose in Verbindung mit anderen Erkrankungen, Leipzig, 1937 Georg Thieme.

<sup>75</sup>Shoji, A. Ueber die langen Cilien bei Trichiasis, *Acta. soc. Ophthalm.* J. g. 36 473-483, 1931; Ed. 46-61.

<sup>76</sup>Bogen, K. Red Hair and Tuberculosis, *Am. Rev. Tuberc.* 63 383-397 1941.

<sup>77</sup>Babarczy, M. V. Hautgefäßdruck bei Lungentuberkulose *Stoch. f. Tuberk.* 86 123-144 1933.

<sup>78</sup>Stefan, W. and Glagoleva, M. Untersuchungen am Capillarnet bei Tuberkulose im Zusammenhang mit den kassierten kassierten Angaben, *Beit. z. Klin. d. Tuberk.* 73: 641-656, 1970.

conditions is well known. The discussion of these relations belongs to the province of allergy.

The lunulae of the *fingernails* were found absent from all fingernails five times more frequently in patients with pulmonary tuberculosis than in controls and eleven times more often when the tuberculosis was complicated by *silicosis*.<sup>44</sup> Heller considers the disappearance of the lunulae an important diagnostic and prognostic sign but it is not rarely seen in healthy person.

*Clubbing* of the fingertips often accompanies chronic pulmonary lesions e.g. emphysema, pulmonary abscess, bronchiectasis and carcinoma.<sup>45</sup> Clubbing occurs in 17 per cent of cases of chronic pulmonary tuberculosis. It seems more



FIG. 236.—Clubbed fingers, bronchiectasis.

common in Negr. males than in whites and it indicates a poor prognosis.<sup>46</sup> The terminal phalanges become thicker and the nails larger and curved in both the longitudinal and transverse directions.

*Puffing* of the nails was observed in 100 per cent of a group of patients suffering from active pulmonary tuberculosis as compared with 6 per cent of a group of patients whose disease had been inactive for a relatively short period. It was completely absent in patients who were inactive for longer than one year.<sup>47</sup>

Frequent dermal lesions of pulmonary tuberculosis are *thickening of the nail plate* and *longitudinal ridging*. The latter is known as the *Hippocratic nail* because Hippocrates knew and described the curved nail and its ominous prognostic significance. Modern observations<sup>48, 49</sup> have amply confirmed the high

<sup>44</sup>Baayal, A. L. andadden, A. V. Tuberculous Changes in Fingernails. Arch. f. Derm. u. Syph. 48, 306-309, 42.

<sup>45</sup>Kaplan, B. H. and Mason, L. Clubbed Fingers in Pulmonary Tuberculosis. Am. Rev. Tuberc. 64, 430-436, 1.

<sup>46</sup>Hjorth, A. O. Change in the Finger Nails in Pulmonary Tuberculosis. Am. Rev. Tuberc. 20, 878-891, 880.

incidence (76 per cent<sup>3110</sup>) of Hippocratic curvature in active cases. Szántó<sup>701</sup> however found only 5.6 per cent among 27,540 patients.

Cyanosis of the distal end of the fingernail bed was noted in 66 per cent of Hahn's group and in 4.2 per cent of Szántó's group of active cases. Differences in the severity of the cases of pulmonary tuberculosis seem to explain the great discrepancy. The cyanosis of the nailbeds is more pronounced in rapidly advancing cases. Ridging transverse and longitudinal does not seem to be of prognostic importance.<sup>702</sup>





# FRUITUS

# MISCELLANEOUS

Secret King despatch-  
ion

Mottling of extremities, milia-  
ri, edema, rarely erythema  
perforans. Great  
hemorrhage, de not blanch  
on pressure; (Pavlov's sign)  
elbow, knee

Toxic Ery-  
thema  
toxic

Mucous atrophy of sup-  
ra. Always at  
regeneration





TABLE II. DERMAL PIGMENTATIONS

CAUSE	DERMAL TON	COLOR	RECURS	ASSOCIATED STRIPINGS	BLOOD	LIVE	PROVINT	HISTORY COURSE	UNUSUALNOTES
Adrenoc. Disease	U splanchnic nervously pigmented area, face bonds. Palms, nail beds, lips, areolar dark	Gray-tan	White spots com- mon	Adrenoc. in petroleum, dehydrat- ion, effect of NaCl and cortis- tine skin	High NaCl High NaCl	High NaCl	Udder is heavily of epidermis, also in cortex (melano- phores)	Chronic with acute attacks	TR. a 30~ scars pig- mented loss of po- tic and axillary hair. Depigmenta- tion rare great ir- regularity
Exophthalmos Ocular	Adrenocortical type or chlo- asma	All degrees	Rare	Vitiligo about 10~					Melanoderma in 14~ mostly mild
Melanin	Adrenocortical type	Gray-tan	Rare	Asymmetrical melanin					
Tuberous	Nipples, areolar, chlo- asma Also Adrenocortical type	Brown	Rare	Cachectic					
Pigmentation and other anomalies in skin spots, freckles	Adrenocortical type diffuse in face per cent	All shades to Brown deep brown	Rare	In some also patches and small pigment spots besides generalized melanoderma			Melanin and iron con- taining pigment	Pigmentation con- fined by ex- posed skin	Rare
Seborrheic Dermatitis	Udder, patchy black, dark, covered areas more involved than bonds or areolar	Gray	Occasionally white spots on bonds, areolar and tongue	Slightly lowered or normal blood pressure. Strikingly depigmented areolar areas. Thick skin. Pe- dicles	Abundant common	Abundant common		Vaginary defect. Melanoderma bonds quickly under hor- pinal care	Common. Diffuse and severe melano- derma rare



TABLE II  
Derivates Polyvinylalcohol—Cellulose

CASE	SYMPTOMS	COLORE	ECZEMAS	ASSOCIATED SYMPTOMS	BLOOD	URINE	PRESENT	HISTORY CONTENTS	MISCELLANEOUS
Melanosis	Face, hands	Brown-black (very rare)		Lymphomas			Melanin		Severe cases extremely rare. Right melanoderma not rare
Hutchinson & Duncan	Abdomen type			Cyanosis, symptoms from debility of the cardiac system and decompensation			Hemosiderin		In 10% of the cases
Chromola-Cerebratory Dermatitis	Extremities, dorsum of hands	Brown		Occasional paralytic of peripheral nerves with course of peripheral nerves			Melanin	Associated cases rare	Protracted cases rare
Kalishina Schenker and others	Abdomen type	AB shades	Spots, diffuse or punctate oral and conjunctival pigmentation common in all races inclined to pigmentation (Mediterranean, Malaya, Indians, Japanese, etc.)					Associated cases rare	Protracted cases rare
Arabic, Argentinians	Diffuse or in small spots around the periphery of the face, "melasma"	Gray-brown	Usually free	Keratinosis, polykeratosis, etc.		As	Melanin, not as	Indolence, const. M. or may not disappear after illumination of As	Exfoliation, Discoloration after Pinta. Severe melanoderma may follow extensive dermatitis from streptococcal infection





TABLE III. DRYGANS YELLOW PRESENTATIONS

(Some data from Jegiers, New England J Med., 1946)

CAUSE	DESCRIPTION	COLORE	STOMACH	ASSOCIATED SYMPTOMS	BLOOD	URINE	LABORATORY TESTS	HISTORY COURSE	REMARKS/NOTES
Liver Diseases	1 Icterus, diffuse 2 Cholelithiasis, localized	Yellow-green, brown Brown spots after particular meals It is not obligatory but relatively common	Serous yellow	Lower cholelithiasis, peritonitis	Serous yellow	Dark	Icteric index higher than 5	Depends on liver trouble	
Cardiorenal	Pallor, plethora, also anemia, etc., also diffuse	Light yellow	Serous white		Serous colorless cardiac	Pale, sometimes cardiac	Cardiorenal is serum or urine	Diagnosis. History of Rule out icterus regurgitates diet, esp. carrots, squashes, etc.	
Alkaline	Diffuse, mostly on dorsa of hands and feet, face, forehead, E. periorbital parts	Yellow	Serous white. Erythematous patches. Erythematous patches (occasionally)		Normal	Pale		Malaria prophylaxis or treatment	Is confined to erythematous patches, patches less yellow than dorsa of the hands
Myxedema	Resembling cardiorenal to lack the yellow discoloration is probability due	Old rose. Pale yellow				Pale	Cardiorenal may be increased in serum and urine		
Stomach Diseases		Very pale yellowish		Cachectic					
Uremia	Face, hands	Pale, yellow-brown				Pale	Urinary chromatogen, possibly increased by uremia		
Diarrhoeal	Entire skin	Pale yellow	Serous yellow		Serous yellow	Pale		Indication of slight Oral hypoglycemia or from phosphoric acid saline	
Phosphoric Acid	Entire skin	Yellow	Serous yellow	Coating, diarrhea		Normal to orange			

TABLE IV. HIRSHUTISM (Hypertichoidism)

	SEX	ONSET	II PERTICHOIDISM	ASSOCIATED SYMPTOMS	LABORATORY TESTS	TREATMENT
Hypertichoidism with adrenocortical hyper- function (J. Spill)	Adult	Both	Puberty	Face chin, upper lip, breasts, ab- domen legs	None. Menstruation nor- mal	Common. Female patients em- barrassed often depressed. Psycho- therapy. Blushing. Shaving etc. Electrolysis. Dis- tributive epilation
	Adult	Female	Adolescence	Bristles about chin		
Hypertichoidism with adrenocortical hyper- function (J. Spill)	Adult	Female	Adolescence	Often male disor- der of puber- tary body hair	Menstrual disorders. Abor- tion. Sterility. Obesity Hirsutism. Diabetes. Acromegaly features	Urinary probe too high too low or normal. Hypertichoidism. Endometrial biopsy. Biopsy be- fore measures taken. Absence of pregnastational changes. Study of vaginal secretions after Papani- cola and Schott
	Adult	Female	Adolescence	Axillary and pubic hirsutism	Breasts underdeveloped long (eunuchoid) extremities Amenorrhea sterility. In- fertility genitalia. Nipple	Rare
Pregnancy		Female		Increased lanugo somewhat hirsutism. Rarely conspicuous	Other signs of pregnancy	
Adrenal cortical hyper- function (hyper- plasia)	Both	Both	Both	Face, arms, legs, breasts, protru- sion of ears, male distribution of hairs, etc.	Hyperpigmentation. Preco- cious puberty. Obesity Diabetes. Coarsening of features	Increased androgenic (17-OH- steroid)

T ALL V THE SKIN IN REL TR X TO AGE

AGE	MICROSCOPIC, TC	MACROSCOPIC PER WRINKLES AND FOLDS	HAI	WINGILLARYOUS
New born	Epidermis thin. Cells small & thin throughout epidermis. Cornium red in color.	Hemorrhagic tendencies. Vaginal bleedng activity of breasts. Pigmentated linea alba. Telangiectatic tendency esp in gls. Hypertrophy of gums and other sympt due to estrogenic maternal influence. Crowled nose of male.		Lack of nerve reactivity. Sebaceous and sweat glands little active.
12	Apocrine glands active. Sebaceous glands develop.		Female ilary hair precedes menarche. Differentiation of sex characters. Shaven becomes necessary male.	Concedones. Vene. All narche.
20	Elasticity cutis peak.			
25		Forehead, nasolabial folds.		Lines on dorsa of hands.
30		Crown feet & lateral angles of the ears.	Peak of hair growth of beard, chest, arms, hands. Occipital baldness becomes less sharp. Graying temples.	
35		Presenile. wrinkles more & length and number.		
40	Thinning of epidermis in spots of local keratotic tendency. Reduction of stratum granulosum and spinosum. Retraction of cutis.	Cervical fold. Suborbital. Cervical folds. Lips become thinner.		All senile changes more marked in skin exposed to light (face, dorsa of arms).
45	Decreased number of sebaceous glands. Papilla flattened. Collagen fibers thinner. Elasticity changes start in the early forties.		Male bush eyebrows or single long hairs. Female, hypertrichosis of chin.	Hypertrophies, small h. mangiform s. come on gradually.

50	Reductions of submaxillary glands Atrophy of areolar muscles	Bridges of nose, ear lobes, chin, hands	Grayling marked	Metacarpal changes
55	Upper eyelids lowered Less reactivity to lower cramped sensibility for touch, pain, temperature	Cutis homobasalis marked. Wrinkles of nose, ear chin hands, cervical folds now marked		Hypopigmented spots. Dry nose. Teeth appear longer
60	Clavicles alternations marked	Radial wrinkles around mouth cheeks droopy	Pubic hair 1 male less curl  Hair growth 1 ear ducts, nose- trils, nape, esp. in male, more conspicuous	Purpura senilis. Penile skin rubbed, darker. Scrotum longer black
65				Atrophy of vulva. Arcus senilis cor- neae. F t hips, thi limbs esp. in female
70		Facial wrinkles crowding. Fold lifted from hand returns along	Head hair often thin or bent	Hypopigmented thoma, keratoma, etc., abundant
75		Lips thin vermilion disappears. Mouth longer swollen Wrinkling of back of hands em marked		N if growth reduced. Tonsil often thickened or deformed
80		Drooping peribul Radial circumoral wrinkles conspicuous, cervical folds em marked. Ears larger longer flabby abruptness Nose seems longer		Tired look. Bony hand

TABLE VI. HYDROLYZING DAYS AND  
Cumpled After Quack, Haden and Other Sources

[illegible]

TABLE VII PRURITUS

Itching, localized or generalized, spontaneous or on slight provocation like exertion, change of temperature, etc., without noticeable skin changes except such as are due to scratching ("Pruritus sine materia")

### I Rule out *Pruritus vulgaris capitis pubis scabies*

Itching & scabies is not always localized to visible lesions. Burrows may be very inconspicuous. Urticarial lesions may have vanished. Consider allergy to plants, paints, wool, silk, external medicaments, soaps, cleansers, cosmetics, flowers, occupational contact allergens, insecticides, fertilizers, garden sprays, etc.

### II Endogenous pruritus

**Diabetes.** If urinary sugar negative, do blood sugar test. If fasting glucose below 120 mg %, glucose tolerance test necessary.

**Gout.** Hyperuricemia. Attacks of arthritis. Tophi.

**Subhepatic disease.** Van den Bergh test. Icterus index. Gall bladder.

**Uremic Disease.** Kidneys. Uremia. Hypertrophy of prostate. Urethral stricture.

**Arteriosclerosis.** Senile pruritus.

**Hypertension.** esp sudden increase of blood pressure.

**Gastrointestinal disease.** Hypacidity constipation diarrhea, typhoid. Helminths.

**Lymphoblastomas.** Leukemia, Hodgkin disease. Mycosis fungoides before eruptions.

**Anemia.**

**Visceral cancer.**

**Focal infection.** Teeth tonsils, prostate, gall bladder.

**Drugs.** Morphine, barbiturates, arsenicals, laxatives, balsamica sulfa-drugs, gold bismuth injections, cocaine, tropic etc.

**Food.** Seafood strawberry wheat chocolate vanilla, mustard and other condiments, etc. Too much coffee drinking.

**Endocrine.** Pregnancy. Dysmenorrhea. Menopause. Hyperthyroidism.

**Neurogenic.** Preceding herpes zoster cerebral disease e.g. pruritus of the nose & brain tumor. Tinea.

**Psychogenic.** Paradoxophobia. Pruritus after scabies. Cases of lice or scabies in surroundings. Truly psychogenic cases of pruritus are rare.

**Infections.** Syphilis (rare). Malaria chronica.

**Weather.** Humid, warm weather change of weather.

### Treatment

1. Treat cause if possible.
2. 1-2% phenol zinc—absorbent lotion.
3. Epsom salt and other saline laxatives.
4. Ergotamine tartrate (gynergen)—0.5-1 mg daily over short periods only. Barbiturate.
5. Autohemotherapy foreign protein.
6. Diet. Vegetarian diet—no red meats, no seafood much sugar (Kluger 1944) 2-5 days on tea, toast sugar milk, butter popples only.
7. Starch bath (1 handful of cornstarch to warm bath).
8. Ultraviolet light in suberythema doses.
9. Bloodletting (120-300 cc) in hypertension.
10. Try benadryl and other antihistaminic drugs.



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